NCT #: NCT04201262

TITLE PAGE

Protocol Title: A Phase 3, External Placebo-Controlled, Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of Ravulizumab in Adult Patients with Neuromyelitis Optica Spectrum Disorder (NMOSD)

Protocol Number: ALXN1210-NMO-307

Amendment Number: 2.0

Compound: Ravulizumab (ALXN1210)

Study Phase: 3

Short Title: A Phase 3 Efficacy and Safety Study of Ravulizumab in Adult Patients with NMOSD

Sponsor Name: Alexion Pharmaceuticals, Inc.

Legal Registered Address: 121 Seaport Boulevard, Boston, MA 02210, USA

Regulatory Agency Identifier Number(s)

IND: 144,187

EudraCT: 2019-003352-37

Approval Date: 01 Sep 2021

Sponsor Signatory:

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 09-Sep-2021 | 12:36:03 EDT
[redacted]

09-Sep-2021 | 12:36:22 EDT

[redacted]
Alexion Pharmaceuticals, Inc.

Date

Medical Monitor Name and Contact Information can be found in the Study Contact List distributed to study sites.

INVESTIGATOR'S AGREEMENT

I have read the ALXN1210-NMO-307 study protocol and agree to conduct the study in accordance with this protocol, all applicable government regulations, the principles of the ICH E6 Guidelines for Good Clinical Practice, and the principles of the World Medical Association Declaration of Helsinki. I also agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document History

Document	Date
Amendment 2.0 (Global)	01 Sep 2021
Amendment 1.2 (United Kingdom)	07 Jun 2021
Amendment 1.1 (Germany)	28 Apr 2021
Amendment 1.0 (Global)	06 Jul 2020
Original Protocol	12 Aug 2019

Amendment 2.0 (Global) (01 Sep 2021)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The main purpose of this amendment is to allow a switch in study drug formulation during the Long-term Extension Period, add visits to reflect the Treatment Period of up to 4.5 years, update the statistical methods, and incorporate administrative changes, as appropriate.

Section # and Name	Description of Change	Brief Rationale
Throughout the protocol	Updated amendment number and approval date.	Administrative change.
Section 1.1 Synopsis, Section 1.2 Schema, Section 1.3 Schedule of Activities (SoA), Section 4.3.1 Ravulizumab, Section 8.1.6.1 Ravulizumab	Added the following content to the overall study design: Patients may be switched from the 10 mg/mL to the 100 mg/mL formulation of ravulizumab with no change to the weight-based dose regimen during the Long-Term Extension Period.	To provide language that allows patients to be switched from the 10 mg/mL to the 100 mg/mL formulation of ravulizumab.
Section 1.1 Synopsis, Section 1.2 Schema, Section 4.1 Overall Design, Section 4.2.3 Rationale for the Duration of the Primary Treatment Period, Section 4.4 End of Primary Treatment	Changed the term “relapse” to “On-trial Relapse” when defining the end of the Primary Treatment Period.	To improve clarity.
Section 1.3 Schedule of Activities (SoA)	Added study visits at Weeks 210, 218, 226, and 234, and added additional SoA table to accommodate new study visits.	To reflect the Treatment Period of up to approximately 4.5 years, with study visits occurring every 8 weeks.
Section 4.2.2.1 Efficacy Endpoints	Changed the term “time to first relapse” to “time to first adjudicated On-trial Relapse” when reference is made to the study endpoint.	To improve clarity.
Section 4.4 End of Primary Treatment, Section 9.3 Populations for Analyses	The mFAS and related text were removed.	In response to regulatory feedback.
Section 6.1	Added 100 mg/mL dose strength.	To align with the change allowing patients to be switched to the

Section # and Name	Description of Change	Brief Rationale
		100 mg/mL formulation of ravulizumab.
Section 6.5.1.3 Standardized Treatment for Relapse	Added text clarifying that treatment for relapse is ultimately at the discretion of the Investigator.	To improve clarity.
Section 8.2.5 Expanded Disability Status Scale (EDSS), Section 8.2.5.1 Expanded Disability Status Scale, Section 8.2.5.2 Functional Systems Scores, Section 10.6 Appendix 6: Expanded Disability Status Scale (EDSS)	Revised text clarifying the EDSS.	To more completely describe the EDSS evaluation performed in the trial.
Section 8.2.10.3 Visual Acuity	Clarified the Landolt C assessment procedure.	To provide clarity regarding the visual acuity measurement process in the trial.
Section 8.3.3 Vital Signs	Clarified that body temperature may be oral, temporal, or axillary.	To provide clarity on methods allowed for temperature assessment.
Section 9.1 Statistical Hypotheses	The hypothesis statement for the adjudicated On-trial ARR is revised from emphasis on the upper 95% confidence interval to being based on the mean adjudicated On-trial ARR.	To provide a hypothesis consistent with a 2-sided p-value approach for this endpoint.
Section 9.2 Sample Size Determination	Changed the term “time to first relapse” to “time to first adjudicated On-trial Relapse.”	To improve clarity.
Section 9.4 Statistical Analysis; and 9.5 Interim Analysis	Added that immunogenicity study data will be included in the final analysis of the Primary Treatment Period.	Added for completeness.
Section 9.4.1 Efficacy Analyses	Removed the statement that the mFAS would be the primary analysis set to account for potential differences resulting from missed or delayed dosing due to the COVID-19 pandemic. Also clarified that sensitivity analyses would account for baseline imbalances between the treatment groups.	Removed the mFAS in response to regulatory feedback and added sensitivity analysis statement for clarity.
Section 9.4.1.1 Primary Endpoint	Added that Firth’s Penalized Likelihood will be used to estimate the hazard ratio, risk reduction, and the profile likelihood 95% CIs if there is no observed event in a treatment arm.	Added for clarification of analysis.
Section 9.4.1.1 Primary Endpoint	Added language on censoring.	Added for clarification of analysis.
Section 9.4.1.2 Secondary Endpoint(s)	Added a statement regarding how the change from baseline to the 6-week post-relapse/EOPT Period analysis time point will be calculated for patients who missed a dose for reasons related to COVID-19.	Added to address potential impact of COVID-19 pandemic on study results.
Section 9.4.1.2.1 Adjudicated On-trial ARR	Changed the language regarding what would be considered statistically significant from the 95% CI approach to	Reframed analysis from 95% CI approach to 2-sided p-value approach

Section # and Name	Description of Change	Brief Rationale
	the 2-sided p-value approach. Also added language to describe how the ARR will be calculated in the event that a patient missed a dose for COVID-19 related reasons.	and added details in the calculation for clarity.
Section 9.4.1.2.2 EuroQoL 5 Dimension (EQ-5D) Index Score and EQ-5D VAS	The nonparametric ANCOVA approach described for analysis of the EQ-5D endpoints is replaced with an ANCOVA on the ranks of the change from baseline in which treatment is a factor and the ranks of the baseline values is a covariate.	Changed to use an analysis more suitable for a nonrandomized trial.
Section 9.4.1.2.5 Accounting for Multiple Comparisons	Removed reference to the upper 95% CI when describing statistical significance.	Reframed analysis of ARR from 95% CI approach to 2-sided p-value approach.
Section 10.1.3 Informed Consent Process	Removed the term "his/her legally authorized representative" and content related to this term when regarding enrollment.	Based on enrollment criteria, patients participating in this study are capable of providing consent. Therefore, content related to legally authorized representative is removed from the informed consent process. Enrollment is closed, and no incapacitated patients were enrolled.
Section 10.1.8 Study and Site Start and Closure	Added the conditions below to the list of reasons for site early closure or termination: • Withdrawal of the favorable opinion or the approval • Inability to adjust the required maximum sum of insurance	To specify additional criteria that may result in study termination.
Section 10.16, Appendix 16 Remote Source Data Verification During COVID-19 Pandemic	Added description of remote source data verification during COVID-19 pandemic.	Use of remote source data verification when onsite study monitoring activities are restricted is being implemented to ensure study integrity.
Section 10.17, Appendix 17 COVID-19 Risk Assessment	Added COVID-19 risk assessment language.	Section newly added to provide potential risks identified and mitigation measures put in place in light of the COVID-19 pandemic
Section 10.18 Appendix 18: Protocol Amendment History	Updated to reflect protocol amendment history.	Administrative change.
Throughout the document	Minor grammatical, editorial, and document formatting revisions, including renumbering of Appendices 16 through 19.	To enhance clarity.

AE = adverse event; ANCOVA = analysis of covariance; ARR = annualized relapse rate; CI = confidence interval; COVID-19 = coronavirus disease 2019; EOPT = End of Primary Treatment; EQ-5D = European Quality of Life Health 5-item questionnaire; EQ VAS = European Quality of Life Visual Analog Scale; mFAS = modified Full Analysis Set; SAP = Statistical Analysis Plan

TABLE OF CONTENTS

TABLE OF TABLES

TABLE OF FIGURES

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 3, External Placebo-Controlled, Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of Ravulizumab in Adult Patients with Neuromyelitis Optica Spectrum Disorder (NMOSD)

Short Title: A Phase 3 Efficacy and Safety Study of Ravulizumab in Adult Patients with NMOSD

Rationale:

Neuromyelitis optica spectrum disorder (NMOSD) is an ultra-rare, severe, disabling autoimmune inflammatory disorder of the central nervous system (CNS) that predominantly affects the optic nerves and spinal cord. In June 2019, the U.S. Food and Drug Administration (FDA) approved SOLIRIS® (eculizumab), a first-generation complement inhibitor, for the treatment of NMOSD in adult patients who are anti-aquaporin-4 (AQP4) antibody (Ab) positive. Findings from the clinical development program of eculizumab in patients with NMOSD support the rationale for complement component 5 (C5) inhibition as a therapeutic approach for reducing the risk of relapses in NMOSD. Ravulizumab has a longer elimination half-life than eculizumab while binding the same epitope on C5, which enables an extended dosing interval while maintaining the high degree of specificity for C5 achieved by eculizumab in inhibiting terminal complement activity.

Given that eculizumab has been proven to reduce the risk of relapse in adult patients with NMOSD, and considering the similar mechanism of action and binding site between ravulizumab and eculizumab, this study is being undertaken to evaluate the efficacy and safety of ravulizumab in adult patients with NMOSD. The goal of this study is to provide NMOSD patients with a treatment option that reduces overall treatment burden by requiring less frequent infusions relative to eculizumab, while maintaining a comparable benefit/risk profile.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the effect of ravulizumab on adjudicated On-trial[a] Relapses in adult patients with NMOSD	• Time to first adjudicated On-trial Relapse and relapse risk reduction
Secondary	
• To evaluate the safety of ravulizumab in adult patients with NMOSD	• Incidence of treatment-emergent adverse events (TEAEs), Treatment-emergent serious adverse events (TESAEs), and TEAEs leading to study drug discontinuation
• To evaluate the effect of ravulizumab on adjudicated annualized relapse rate (ARR) in adult patients with NMOSD	• Adjudicated On-trial ARR
• To evaluate the effect of ravulizumab on disease-related disability in adult patients with NMOSD	• Clinically important worsening from baseline in expanded disability status scale (EDSS)
• To evaluate the effect of ravulizumab on quality of life (QoL) in adult patients with NMOSD	• Change from baseline in EuroQoL-5D (EQ-5D)

Objectives	Endpoints
• To evaluate the effect of ravulizumab on neurologic function in adult patients with NMOSD	• Clinically important change from baseline in Hauser ambulation index (HAI)
• To characterize the pharmacokinetics (PK) of ravulizumab in adult patients with NMOSD	• Change in serum ravulizumab concentration over the study duration
• To characterize the pharmacodynamics (PD) of ravulizumab in adult patients with NMOSD	• Change in serum free C5 concentration over the study duration
• To characterize the immunogenicity of ravulizumab in adult patients with NMOSD	• Presence and titer of anti-drug antibodies (ADAs) over the study duration
[a] On-trial Relapses refer to relapses as determined by the Treating Physician that occur during the study treatment period. All relapses will be adjudicated by a separate Adjudication Committee	

Overall Design

Study ALXN1210-NMO-307 is a Phase 3, external placebo-controlled, open-label, multicenter study to evaluate the efficacy and safety of ravulizumab in adult patients with NMOSD. Approximately 55 eligible adult patients with NMOSD will be enrolled.

This study will employ a single-arm treatment design, utilizing the placebo group from Study ECU-NMO-301 (conducted 2014 to 2018) as an external placebo control. This will allow for a robust assessment of ravulizumab as a treatment option for NMOSD.

There are 4 periods in this study: Screening Period, Primary Treatment Period, Long-Term Extension Period, and Safety Follow-up Period. Patients will be screened for eligibility for up to 6 weeks during the Screening Period. The end of the Primary Treatment Period will be triggered when either (1) 2 patients have had an adjudicated On-trial Relapse; or (2) all patients have completed, or discontinued prior to, the Week 26 Visit; whichever comes later. However, if 2 patients have not had an adjudicated On-trial Relapse by the time all patients have completed, or discontinued prior to, the Week 50 visit, the end of the Primary Treatment Period will be triggered at that time. Note that patients who complete the visits indicated above (Week 26 or Week 50) will remain on the study in the Primary Treatment Period until the Primary Treatment Period ends. For examples of different scenarios of the end of the Primary Treatment Period, please refer to Section 4.4. Based on the estimated enrollment rate, the duration of the Primary Treatment Period for each patient is expected to be between 26 weeks and approximately 2.5 years. The Primary Treatment Period ends and the Long-Term Extension Period starts when all patients have completed their End of Primary Treatment (EOPT) Visit within the timeframe specified in Section 4.4. All patients will continue to receive ravulizumab during the Long-Term Extension Period for up to approximately 2 years, or until ravulizumab is approved and/or available (in accordance with country-specific regulations), whichever occurs first. The total treatment duration for each patient will be up to approximately 4.5 years. After the last dose of study drug or early discontinuation (ED), patients will be followed for 8 weeks.

Disclosure Statement: This is a single-arm treatment study with no masking.

Number of Patients:

Approximately 55 eligible patients will be enrolled.

Study Drug Groups and Duration:

Eligible patients will enroll into the study to receive intravenous infusions of ravulizumab.

The ravulizumab dose for each patient will be based on body weight. The dosing regimen consists of a loading dose followed by maintenance dosing administered every 8 weeks (q8w). The maintenance dosing should be initiated 2 weeks after the loading dose administration. Patients may be switched from the 10 mg/mL to the 100 mg/mL formulation of ravulizumab with no change to the weight-based dose regimen during the Long-Term Extension Period.

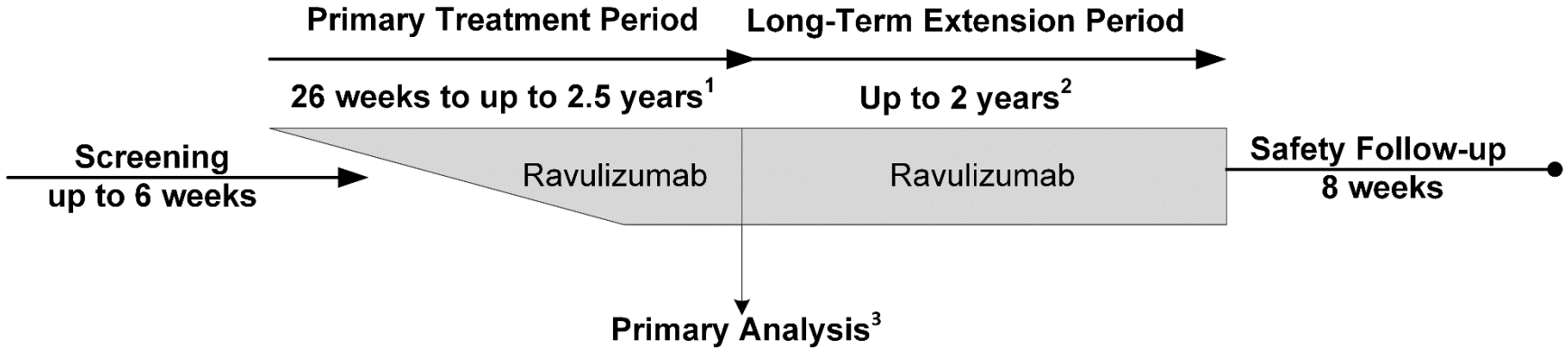
For each patient, the total duration of study participation will be up to approximately 4.75 years, including the Screening Period (up to 6 weeks), the Primary Treatment Period (between 26 weeks and approximately 2.5 years), the Long-Term Extension Period (up to approximately 2 years), and the Safety Follow-up Period (8 weeks).

Data Monitoring Committee: No

Relapse Adjudication Committee: Yes

1.2. Schema

Figure 1 Study ALXN1210-NMO-307 Schematic



[1]All eligible patients will receive open-label ravulizumab during the Primary Treatment Period. The end of the Primary Treatment Period will be triggered either when (1) 2 patients have had an adjudicated On-trial Relapse; or (2) all patients have completed, or discontinued prior to, the Week 26 Visit; whichever comes later. However, if 2 patients have not had an adjudicated On-trial Relapse by the time all patients have completed, or discontinued prior to, the Week 50 visit, the end of the Primary Treatment Period will be triggered at that time. Note that patients who complete the visits indicated above (Week 26 or Week 50) will remain on the study in the Primary Treatment Period until the Primary Treatment Period ends. Based on the estimated enrollment rate, the duration of the Primary Treatment Period for each patient is expected to be between 26 weeks and approximately 2.5 years.

[2] The Primary Treatment Period ends and the Long-Term Extension Period starts when all patients have completed their End of Primary Treatment (EOPT) Visit within the time frame specified in Section 4.4. Patients will continue to receive ravulizumab during the Long-Term Extension Period for up to approximately 2 years, or until ravulizumab is approved and/or available (in accordance with country-specific regulations), whichever occurs first.

[3]The primary analysis for regulatory submission will be conducted at the end of the Primary Treatment Period, and will include all available efficacy, safety, and PK/PD/ADA data collected from the Primary Treatment Period.

Note: Patients may be switched from the 10 mg/mL to the 100 mg/mL formulation of ravulizumab with no change to the weight-based dose regimen during the Long-Term Extension Period.

1.3. Schedule of Activities (SoA)

Table 1: Schedule of Activities (Screening Through Week 58)

	Screening	Treatment											Notes
Visit[1]	**W-6 to -1**		**W2**	**W6**	**W10**	**W18**	**W26**	**W34**	**W42**	**W50**	**W58**	**Phone**[2]	**Additional evaluation visits can be scheduled at the discretion of the Investigator. An ED Visit should be performed if patients discontinue early**
Days and Window		**D1**	**D15 ± 2**	**D43 ± 2**	**D71 ± 2**	**D127 ± 2**	**D183 ± 2**	**D239 ± 7**	**D295 ± 7**	**D351 ± 7**	**D407 ± 7**		
General Assessments/Procedures													
Informed Consent	X												
Medical History	X												
NMOSD History/Diagnosis	X												
Anti-AQP4 Ab Test (Serum)	X												Refer to Section 5.1 for testing requirements.
Inclusion/Exclusion	X												
Demographics	X												
Weight	X	X	X		X	X	X	X	X	X	X		
Height	X												
N. meningitidis Vaccination	X												Patients must be vaccinated against meningococcal infection, and revaccinated during the study if needed (Section 8.1.4)
HIV Test	X												Test includes HIV-1 and HIV-2
Pregnancy Test (WOCBP only)	X	X	X		X	X	X	X	X	X	X		Serum test at screening is required. Urine test at indicated visits and when necessary at Investigator's discretion
Dispense Patient Safety Card and NMO Symptom Card	X												Instruct patients to carry safety card at all times and bring both cards to scheduled visits (Section 8.2.2; Section 8.3.5)
Pharmacokinetic and Pharmacodynamic Assessments													
PK/Free C5 Blood Samples		B/P	T/P	X	T/P	T/P	T/P	T/P		T/P			Collect B (baseline), T (predose), P (postdose), and X (anytime) samples (Section 8.6)

	Screening	Treatment											Notes
Visit[1]	**W-6 to -1**		**W2**	**W6**	**W10**	**W18**	**W26**	**W34**	**W42**	**W50**	**W58**	**Phone**[2]	**Additional evaluation visits can be scheduled at the discretion of the Investigator. An ED Visit should be performed if patients discontinue early**
Days and Window		**D1**	**D15 ± 2**	**D43 ± 2**	**D71 ± 2**	**D127 ± 2**	**D183 ± 2**	**D239 ± 7**	**D295 ± 7**	**D351 ± 7**	**D407 ± 7**		
PK/Free C5 CSF Samples		B					T						Optional; collect B (baseline) and T (predose) samples from patients who consent to CSF collection (Section 8.6)
ADA Blood Samples		B					T			T			Collect B (baseline) and T (predose) samples (Section 8.9)
Safety Assessments													
Physical Examination	X												
Targeted Physical Examination		X	X	X	X	X	X	X	X	X	X		Perform when deemed necessary by the Investigator (Section 8.3.1)
Vital Signs	X	X	X	X	X	X	X	X	X	X	X		
ECG	X	X					X			X			
Prior Medications	X												
Concomitant Medications	Continuous monitoring												
Concomitant Non-Drug Therapies/Procedures	Continuous monitoring												
AE	Continuous monitoring												
Clinical Laboratory Tests	X	X	X	X	X	X	X		X		X		Refer to Section 10.2 for the list of tests
Patient Safety Card Review		X	X	X	X	X	X	X	X	X	X	X	Review signs and symptoms of infections (Section 8.3.5)
C-SSRS		X		X		X	X		X		X		2 types of C-SSRS assessments: Baseline (Day 1) and Since last visit (Section 8.3.8)
Efficacy Assessments													
Neurologic Examination[3]	X	X	X	X	X	X	X		X		X		
NMO Symptom Card and Evaluation	X	X	X	X	X	X	X	X	X	X	X	X	NMOSD symptoms will be evaluated by the Investigator (Section 8.2.2)

	Screening	Treatment											Notes
Visit[1]	**W-6 to -1**		**W2**	**W6**	**W10**	**W18**	**W26**	**W34**	**W42**	**W50**	**W58**	**Phone**[2]	**Additional evaluation visits can be scheduled at the discretion of the Investigator. An ED Visit should be performed if patients discontinue early**
Days and Window		**D1**	**D15 ± 2**	**D43 ± 2**	**D71 ± 2**	**D127 ± 2**	**D183 ± 2**	**D239 ± 7**	**D295 ± 7**	**D351 ± 7**	**D407 ± 7**		
EQ-5D	X	X		X		X	X		X		X		When possible, administer before other procedures
SF-36	X	X		X		X	X		X		X		When possible, administer before other procedures
EDSS (including FSS)	X	X		X		X	X		X		X		Conducted by a blinded EDSS Rater (Section 8.2.5)
HAI	X	X		X		X	X		X		X		Performed by the Investigator or trained designee
OSIS[3]		X											
Ophthalmological Examination	X	X		X		X	X		X		X		Including confrontational field test[1], color vision and visual acuity (Section 8.2.10)
OCT	X												
MRI	X												Brain, cervical spine, and thoracic spine; contrast is optional
Biomarker Research													
Blood samples		X	X	X			X			X			Blood samples for DNA and RNA are optional; blood sample for DNA is only collected on Day 1.
CSF samples		X					X						Optional
Administration of Study Drug													
Ravulizumab[4]		X	X		X	X	X	X	X	X	X		Administered after all other required tests/procedures, except those to be performed postdosing

[1] Under reasonable occasional circumstances where a patient is not able to attend a study visit on site, a home visit or visit at an alternative healthcare facility may be permitted by the Sponsor after discussing with the Alexion Medical Monitor. This will be a case-by-case decision (Section 8.1.7).
[2] Biweekly phone visit will be conducted between the visits to monitor NMOSD symptoms and safety (Section 8.2.2).
[3] Performed by the Treating Physician who is an Investigator and has been properly trained for the evaluation, preferably the same Treating Physician, throughout the study.
[4] Patients may be switched from the 10 mg/mL to the 100 mg/mL formulation of ravulizumab with no change to the weight-based dose regimen during the Long-Term Extension Period (Section 8.1.6.1).

	Screening	Treatment											Notes
Visit[1]	**W-6 to -1**		**W2**	**W6**	**W10**	**W18**	**W26**	**W34**	**W42**	**W50**	**W58**	**Phone**[2]	**Additional evaluation visits can be scheduled at the discretion of the Investigator. An ED Visit should be performed if patients discontinue early**
Days and Window		**D1**	**D15 ± 2**	**D43 ± 2**	**D71 ± 2**	**D127 ± 2**	**D183 ± 2**	**D239 ± 7**	**D295 ± 7**	**D351 ± 7**	**D407 ± 7**		

Abbreviations: ADA = antidrug antibody; AE = adverse event; AQP4 Ab = aquaporin 4 antibody; B = baseline sample; C5 = complement component 5; CSF = cerebrospinal fluid; C-SSRS = Columbia-suicide severity rating scale; D = day; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ED = early discontinuation; EDSS = expanded disability status scale; EQ-5D = EuroQoL-5D; FSS = functional system score; HAI = Hauser ambulation index; HIV = human immunodeficiency virus; MRI = magnetic resonance imaging; NMOSD = neuromyelitis optica spectrum disorder; OCT = optical coherence tomography; OSIS = optic spinal impairment score; P = postdose sample; PK = pharmacokinetic(s); RNA = ribonucleic acid; SF-36 = short form health survey; T = trough sample; W = week(s); WOCBP = women of childbearing potential

Table 2: Schedule of Activities (Week 66 Through Week 138)

	Treatment											Notes
Visit[1]	**W66**	**W74**	**W82**	**W90**	**W98**	**W106**	**W114**	**W122**	**W130**	**W138**	**Phone**[2]	**Additional evaluation visits can be scheduled at the discretion of the Investigator. An ED Visit should be performed if patients discontinue early.**
Days and Window	**D463 ± 7**	**D519 ± 7**	**D575 ± 7**	**D631 ± 7**	**D687 ± 7**	**D743 ± 7**	**D799 ± 7**	**D855 ± 7**	**D911 ± 7**	**D967 ± 7**		
General Assessments/Procedures												
Weight	X	X	X	X	X	X	X	X	X	X		
N. meningitidis Vaccination												Patients must be vaccinated against meningococcal infection, and revaccinated during the study if needed (Section 8.1.4)
Pregnancy Test (WOCBP only)	X	X	X	X	X	X	X	X	X	X		Serum test at screening is required. Urine test at indicated visits and when necessary at Investigator's discretion
Pharmacokinetic and Pharmacodynamic Assessments												
PK/Free C5 Blood Samples	T/P		T/P			T/P			T/P			Collect T (predose) and P (postdose) samples (Section 8.6)
PK/Free C5 CSF Samples			T						T			Optional; collect sample T (predose) from patients who consent to CSF sample collection (Section 8.6)
ADA Blood Samples			T			T			T			Collect T (predose) samples (Section 8.9)
Safety Assessments												
Targeted Physical Examination	X	X	X	X	X	X	X	X	X	X		Perform when deemed necessary by the Investigator (Section 8.3.1)
Vital Signs	X	X	X	X	X	X	X	X	X	X		
ECG						X						
Concomitant Medications	Continuous Monitoring											
Concomitant Non-Drug Therapies/Procedures	Continuous Monitoring											
AE	Continuous Monitoring											

	Treatment											Notes
Visit[1]	**W66**	**W74**	**W82**	**W90**	**W98**	**W106**	**W114**	**W122**	**W130**	**W138**	**Phone**[2]	**Additional evaluation visits can be scheduled at the discretion of the Investigator. An ED Visit should be performed if patients discontinue early.**
Days and Window	**D463 ± 7**	**D519 ± 7**	**D575 ± 7**	**D631 ± 7**	**D687 ± 7**	**D743 ± 7**	**D799 ± 7**	**D855 ± 7**	**D911 ± 7**	**D967 ± 7**		
Clinical Laboratory Tests		X		X		X		X		X		Refer to Section 10.2 for the list of tests.
Patient Safety Card Review	X	X	X	X	X	X	X	X	X	X	X	Review signs and symptoms of infections (Section 8.3.5)
C-SSRS		X		X		X			X			Conduct C-SSRS-Since Last Visit assessment (Section 8.3.8)
Efficacy Assessments												
Neurologic Examination[3]		X		X		X			X			
NMO Symptom Card and Evaluation	X	X	X	X	X	X	X	X	X	X	X	NMOSD symptoms will be evaluated by the Investigator (Section 8.2.2)
EQ-5D		X		X		X			X			When possible administer before other procedures
SF-36		X		X		X			X			When possible administer before other procedures
EDSS (including FSS)		X		X		X			X			Conducted by a blinded EDSS Rater (Section 8.2.5)
HAI		X		X		X			X			Performed by an Investigator or trained designee
Ophthalmological Examination		X		X		X			X			Including confrontational field test[1], color vision and visual acuity (Landolt C ring) (Section 8.2.10)
Biomarker Research												
Blood samples			X			X			X			Blood samples for RNA are optional
CSF samples			X						X			Optional
Administration of Study Drug												
Ravulizumab[4]	X	X	X	X	X	X	X	X	X	X		Administered after all other required tests/procedures, except those to be performed postdosing

[1] Under reasonable occasional circumstances where a patient is not able to attend a study visit on site, a home visit or visit at an alternative healthcare facility may be permitted by the Sponsor after discussing with the Alexion Medical Monitor. This will be a case-by-case decision (Section 8.1.7).

	Treatment											Notes
Visit[1]	**W66**	**W74**	**W82**	**W90**	**W98**	**W106**	**W114**	**W122**	**W130**	**W138**	**Phone**[2]	**Additional evaluation visits can be scheduled at the discretion of the Investigator. An ED Visit should be performed if patients discontinue early.**
Days and Window	**D463 ± 7**	**D519 ± 7**	**D575 ± 7**	**D631 ± 7**	**D687 ± 7**	**D743 ± 7**	**D799 ± 7**	**D855 ± 7**	**D911 ± 7**	**D967 ± 7**		

[2] Biweekly phone visits will be conducted between the visits to monitor NMOSD symptoms and safety (Section 8.2.2).
[3] Performed by the Treating Physician who is an Investigator and has been properly trained for the evaluation, preferably the same Treating Physician, throughout the study.
[4] Patients may be switched from the 10 mg/mL to the 100 mg/mL formulation of ravulizumab with no change to the weight-based dose regimen during the Long-Term Extension Period (Section 8.1.6.1).
Abbreviations: ADA = antidrug antibody; AE = adverse event; B = baseline sample; C5 = complement component 5; CSF = cerebrospinal fluid; C-SSRS = Columbia-suicide severity rating scale; D = day; ECG = electrocardiogram; ED = early discontinuation; EDSS = expanded disability status scale; EQ-5D = EuroQoL-5D; FSS = functional system score; HAI = Hauser ambulation index; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorder; P = postdose sample; PK = pharmacokinetic(s); RNA = ribonucleic acid; SF-36 = short form health survey; T = trough sample; W = week(s); WOCBP = women of childbearing potential

Table 3: Schedule of Activities (Week 146 Through Week 234)

	Treatment													Notes
Visit[1]	**W 146**	**W 154**	**W 162**	**W 170**	**W 178**	**W 186**	**W 194**	**W 202**	**W 210**	**W 218**	**W 226**	**W 234**	**Phone**[2]	**Additional evaluation visits can be scheduled at the discretion of the Investigator. An ED Visit should be performed if patient discontinues early.**
Days and Window	**D 1023 ± 7**	**D 1079 ± 7**	**D 1135 ± 7**	**D 1190 ± 7**	**D 1247 ± 7**	**D 1303 ± 7**	**D 1359 ± 7**	**D 1415 ± 7**	**D 1471 ± 7**	**D 1527** ± 7	**D 1583** ± 7	**D 1639 ± 7**		
General Assessments/Procedures														
Weight	X	X	X	X	X	X	X	X	X	X	X	X		
N. meningitidis Vaccination														Patients must be vaccinated against meningococcal infection, and revaccinated during the study if needed (Section 8.1.4)
Pregnancy Test (WOCBP only)	X	X	X	X	X	X	X	X	X	X	X	X		Serum test at screening is required. Urine test at indicated visits and when necessary at Investigator's discretion
Pharmacokinetic and Pharmacodynamic Assessments														
PK/Free C5 Blood Samples			T/P				T/P				T/P			Collect T (predose) and P (postdose) samples (Section 8.6)
PK/Free C5 CSF Samples							T							Optional; obtain at predose from patients who consent to CSF sample collection (Section 8.6)
ADA Blood Samples			T				T				T			Collect T (predose) and X (anytime) samples (Section 8.9)
Safety Assessments														
Targeted Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X		Perform when deemed necessary by the Investigator (Section 8.3.1)
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X		
ECG			X							X				
Concomitant Medication	Continuous Monitoring													

	Treatment													Notes
Visit[1]	**W 146**	**W 154**	**W 162**	**W 170**	**W 178**	**W 186**	**W 194**	**W 202**	**W 210**	**W 218**	**W 226**	**W 234**	**Phone**[2]	**Additional evaluation visits can be scheduled at the discretion of the Investigator. An ED Visit should be performed if patient discontinues early.**
Days and Window	**D 1023 ± 7**	**D 1079 ± 7**	**D 1135 ± 7**	**D 1190 ± 7**	**D 1247 ± 7**	**D 1303 ± 7**	**D 1359 ± 7**	**D 1415 ± 7**	**D 1471 ± 7**	**D 1527** ± 7	**D 1583** ± 7	**D 1639 ± 7**		
Concomitant Non-Drug Therapies/Procedures	Continuous Monitoring													
AE	Continuous Monitoring													
Clinical Laboratory Tests		X		X		X		X		X		X		Refer to Section 10.2 for the list of tests
Patient Safety Card	X	X	X	X	X	X	X	X	X	X	X	X	X	Review signs and symptoms of infections (Section 8.3.5)
C-SSRS		X			X			X			X			C-SSRS-Since Last Visit assessment (Section 8.3.8)
Efficacy Assessments														
Neurologic Examination[3]		X			X			X			X			
NMO Symptom Card and Evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X	NMOSD symptoms will be evaluated by the Investigator (Section 8.2.2)
EQ-5D		X			X			X			X			When possible, administer before other procedures
SF-36		X			X			X			X			When possible, administer before other procedures
EDSS (including FSS)		X			X			X			X			Conducted by a blinded EDSS Rater (Section 8.2.5)
HAI		X			X			X			X			Performed by an Investigator or trained designee
Ophthalmological Examination		X			X			X			X			Including confrontational field test[1], color vision and visual acuity (Landolt C ring) (Section 8.2.10).

	Treatment													Notes
Visit[1]	**W 146**	**W 154**	**W 162**	**W 170**	**W 178**	**W 186**	**W 194**	**W 202**	**W 210**	**W 218**	**W 226**	**W 234**	**Phone**[2]	**Additional evaluation visits can be scheduled at the discretion of the Investigator. An ED Visit should be performed if patient discontinues early.**
Days and Window	**D 1023 ± 7**	**D 1079 ± 7**	**D 1135 ± 7**	**D 1190 ± 7**	**D 1247 ± 7**	**D 1303 ± 7**	**D 1359 ± 7**	**D 1415 ± 7**	**D 1471 ± 7**	**D 1527** ± 7	**D 1583** ± 7	**D 1639 ± 7**		
Biomarker Research														
Blood Samples			X				X							Blood samples for RNA are optional
CSF Samples							X							Optional
	Administration of Study Drug													
Ravulizumab[4]	X	X	X	X	X	X	X	X	X	X	X	X		Administered after all other required tests/procedures, except those to be performed postdosing

[1] Under reasonable occasional circumstances where a patient is not able to attend a study visit on site, a home visit or visit at an alternative healthcare facility may be permitted by the Sponsor after discussing with the Alexion Medical Monitor. This will be a case-by-case decision (Section 8.1.7).
[2] Biweekly phone visits will be conducted between the visits to monitor NMOSD symptoms and safety (Section 8.2.2).
[3] Performed by the Treating Physician who is an Investigator and has been properly trained for the evaluation, preferably the same Treating Physician, throughout the study.
[4] Patients may be switched from the 10 mg/mL to the 100 mg/mL formulation of ravulizumab with no change to the weight-based dose regimen during the Long-Term Extension Period (Section 8.1.6.1).
Abbreviations: ADA = antidrug antibody; AE = adverse event; B = baseline sample; C5 = complement component 5; CSF = cerebrospinal fluid; C-SSRS = Columbia-suicide severity rating scale; D = day; ECG = electrocardiogram; ED = Early Discontinuation; EDSS = expanded disability status scale; EQ-5D = EuroQoL-5D; FSS = functional system score; HAI = Hauser ambulation index; NMO = neuromyelitis optic; NMOSD = neuromyelitis optica spectrum disorder; P = postdose sample; PK = pharmacokinetic(s); PT = primary treatment; RNA = ribonucleic acid; SF-36 = short form health survey; T = trough sample; W = week(s); WOCBP = women of childbearing potential

Table 4: Schedule of Activities (End of Primary Treatment, End of Treatment/Early Discontinuation, Follow-Up)

	Treatment		**FU**	**Notes**
Visit[1]	**EOPT**	**EOT/ED**	**FU**	**Additional evaluation visits can be scheduled at the discretion of the Investigator. Refer to Section 4.4 for EOPT. An ED Visit should be performed if patient discontinues early.**
Days and Window	**Within 14 D after PT**			
General Assessments/Procedures				
Weight	X	X		
N. meningitidis Vaccination				Patients must be vaccinated against meningococcal infection, and revaccinated during the study if needed (Section 8.1.4)
Pregnancy Test (WOCBP only)	X	X	X	Serum test at screening is required. Urine test at indicated visits and when necessary at Investigator's discretion
Pharmacokinetic and Pharmacodynamic Assessments				
PK/Free C5 Blood Samples		T/P		Collect T (predose) and P (postdose) samples (Section 8.6)
PK/Free C5 CSF Samples		T		Optional; obtain at predose from patients who consent to CSF sample collection (Section 8.6)
ADA Blood Samples		T		Collect T (predose) and X (anytime) samples (Section 8.9)
Safety Assessments				
Targeted Physical Examination	X	X	X	Perform when deemed necessary by the Investigator (Section 8.3.1)
Vital Signs	X	X	X	
ECG		X		
Concomitant Medication	Continuous Monitoring			
Concomitant Non-Drug Therapies/Procedures	Continuous Monitoring			
AE	Continuous Monitoring			
Clinical Laboratory Tests	X	X	X	Refer to Section 10.2 for the list of tests
Patient Safety Card	X	X	X	Review signs and symptoms of infections (Section 8.3.5)

	Treatment		FU	Notes
Visit[1]	**EOPT**	**EOT/ED**	**FU**	**Additional evaluation visits can be scheduled at the discretion of the Investigator. Refer to Section 4.4 for EOPT. An ED Visit should be performed if patient discontinues early.**
Days and Window	**Within 14 D after PT**			
C-SSRS	X	X	X	C-SSRS-Since Last Visit assessment (Section 8.3.8)
Efficacy Assessments				
Neurologic Examination[2]	X	X	X	
NMO Symptom Card and Evaluation	X	X	X	NMOSD symptoms will be evaluated by the Investigator (Section 8.2.2)
EQ-5D	X	X		When possible, administer before other procedures
SF-36	X	X		When possible, administer before other procedures
EDSS (including FSS)	X	X		Conducted by a blinded EDSS Rater (Section 8.2.5)
HAI	X	X		Performed by an Investigator or trained designee
Ophthalmological Examination	X	X		Including confrontational field test[1], color vision and visual acuity (Landolt C ring) (Section 8.2.10).
Biomarker Research				
Blood Samples		X		Blood samples for RNA are optional
CSF Samples		X		Optional
Administration of Study Drug				
Ravulizumab[3]	X[4]	X		Administered after all other required tests/procedures, except those to be performed postdosing

[1] Under reasonable occasional circumstances where a patient is not able to attend a study visit on site, a home visit or visit at an alternative healthcare facility may be permitted by the Sponsor after discussing with the Alexion Medical Monitor. This will be a case-by-case decision (Section 8.1.7).
[2] Performed by the Treating Physician who is the Investigator and has been properly trained for the evaluation, preferably the same Treating Physician, throughout the study.

	Treatment		FU	Notes
Visit[1]	**EOPT**	**EOT/ED**	**FU**	**Additional evaluation visits can be scheduled at the discretion of the Investigator. Refer to Section 4.4 for EOPT. An ED Visit should be performed if patient discontinues early.**
Days and Window	**Within 14 D after PT**			

[3] Patients may be switched from the 10 mg/mL to the 100 mg/mL formulation of ravulizumab with no change to the weight-based dose regimen during the Long-Term Extension Period (Section 8.1.6.1).

[4] If EOPT visit coincides with a scheduled dosing visit, ravulizumab dose should be administered.

Abbreviations: ADA = antidrug antibody; AE = adverse event; B = baseline sample; C5 = complement component 5; CSF = cerebrospinal fluid; C-SSRS = Columbia-suicide severity rating scale; D = day; ECG = electrocardiogram; ED = Early Discontinuation; EDSS = expanded disability status scale; EOPT = end of primary treatment; EOT = end of treatment; EQ-5D = EuroQoL-5D; FSS = functional system score; FU = follow-up; HAI = Hauser ambulation index; NMO = neuromyelitis optic; NMOSD = neuromyelitis optica spectrum disorder; P = postdose sample; PK = pharmacokinetic(s); PT = primary treatment; RNA = ribonucleic acid; SF-36 = short form health survey; T = trough sample; W = week(s); WOCBP = women of childbearing potential

Table 5: Schedule of Activities (Relapse Evaluation Period)

	Relapse Evaluation Period					Notes
Visits	**Relapse Evaluation Visit**	**Relapse FU Visits**				**Every effort must be made to evaluate potential relapses within 24 hours of notification of the Investigator of a possible relapse, and no later than 48 hours.**
Weeks	**Within 24 to 48 hours**	**+1 Week**	**+4 Weeks**	**+6 Weeks**	**Unscheduled[1]**	
Days and Window	**RD1**	**RD8±2**	**RD29±2**	**RD43±2**	**NA**	
General Assessments/Procedures						
Anti-AQP4 Ab (serum)	X			X	X	
Pharmacokinetic and Pharmacodynamic Assessments						
PK/Free C5 Blood Samples	X	X	X	X	X	Refer to Section 8.6 for sample collection during relapse
Safety Assessments						
Vital Signs	X	X	X	X	X	Vital signs will also be collected during relapse visits when study drug is administered
Concomitant Medication	Continuous Monitoring					
Concomitant Non-Drug Therapies/Procedures	Continuous Monitoring					
AE	Continuous Monitoring					
Pregnancy Test (WOCBP only)						Perform urine test when study drug is administrated at a relapse visit
Clinical laboratory Tests	X			X	X	Refer to Section 10.2 for the list of tests
Patient Safety Card	X	X	X	X	X	Review signs and symptoms of infections (Section 8.3.5)
C-SSRS				X		Conduct C-SSRS-Since Last Visit assessment (Section 8.3.8)
Efficacy Assessments						
Neurologic Examination[2]	X	X	X	X	X	
NMO Symptom Card and Evaluation	X	X	X	X	X	NMO symptoms will be evaluated by the Treating Physician (Section 8.2.2)

	Relapse Evaluation Period					Notes
Visits	**Relapse Evaluation Visit**	**Relapse FU Visits**				**Every effort must be made to evaluate potential relapses within 24 hours of notification of the Investigator of a possible relapse, and no later than 48 hours.**
Weeks	**Within 24 to 48 hours**	**+1 Week**	**+4 Weeks**	**+6 Weeks**	**Unscheduled[1]**	
Days and Window	**RD1**	**RD8±2**	**RD29±2**	**RD43±2**	**NA**	
EQ-5D	X	X	X	X	X	When possible, administer before other procedures
SF-36	X	X	X	X	X	When possible, administer before other procedures
EDSS (including FSS)	X	X	X	X	X	Conducted by a blinded EDSS Rater (Section 8.2.5)
HAI	X	X	X	X	X	Performed by an Investigator or trained designee
OSIS[2]	X	X	X	X	X	
Ophthalmologic Examination	X	X	X	X	X	Including confrontational field test[2], color vision and visual acuity (Landolt C ring) (Section 8.2.10)
MRI	X					Perform if deemed clinically necessary by the Investigator (Section 8.2.11)
OCT	X					Perform if deemed clinically necessary by the Investigator (Section 8.2.11)
Biomarker Research						
Blood Samples	X	X		X	X	Blood samples for RNA are optional.
CSF samples	X					Optional
Administration of Study Drug						
Ravulizumab						Refer to Section 8.1.6 for the instruction of study drug administration during relapse

[1] Additional unscheduled Follow-up Relapse Evaluation Visits are permitted at the discretion of the Investigator.
[2] Performed by the Treating Physician who is an Investigator and has been properly trained for the evaluation, preferably the same Treating Physician, throughout the study.
Abbreviations: ADA = antidrug antibody; AE = adverse event; AQP4 Ab = aquaporin 4 antibody; C5 = complement component 5; CSF = cerebrospinal fluid; C-SSRS = Columbia-suicide severity rating scale; EDSS = expanded disability status scale; EQ-5D = EuroQoL-5D; FSS = functional system score; FU = follow-up; HAI = Hauser ambulation index; MRI = magnetic resonance imaging; NA = not applicable; NMO = neuromyelitis optica; OCT = optical coherence tomography; OSIS = optic spinal impairment score; PK = pharmacokinetic(s); RD = relapse day; RNA = ribonucleic acid; SF-36 = short form health survey; T = trough sample; W = week(s); WOCBP = women of childbearing potential

2. INTRODUCTION

Complement activation is a key element in the development of CNS injury in neuromyelitis optica spectrum disorder (NMOSD). Ravulizumab is a recombinant, humanized monoclonal antibody (mAb) with high specificity against human complement component 5 (C5). It is currently being developed as a treatment for NMOSD in adult patients.

2.1. Study Rationale

The basis of developing ravulizumab for NMOSD stems from prior experience with eculizumab (SOLIRIS®), a first-generation complement inhibitor, which is approved by the U.S. FDA for the treatment of NMOSD in adult patients who are anti-AQP4 Ab positive. Findings from the clinical development program for eculizumab in NMOSD support the rationale for C5 inhibition as a therapeutic approach for reducing the risk of relapses in patients with NMOSD (Pittock SJ, 2019).

Ravulizumab shares > 99% amino acid sequence homology with eculizumab. Ravulizumab and eculizumab share the same mechanism of action, targeting the same C5 epitope with high specificity. However, as a result of 4 amino acid substitutions, the serum elimination half-life of ravulizumab is prolonged, enabling an extended dosing interval. Despite a longer dosing interval, ravulizumab has demonstrated a similar degree of terminal complement inhibition compared to eculizumab in patients with paroxysmal nocturnal hemoglobinuria (PNH), another complement-mediated disease, for which both products are approved in the US. Complement inhibition is the only mechanism of action of eculizumab in NMOSD, and the fact that it has been proven to significantly reduce the risk of relapse provides a strong rationale for studying ravulizumab in NMOSD.

This study is being undertaken to demonstrate the efficacy and safety of ravulizumab in adult patients with NMOSD, using the placebo group from Study ECU-NMO-301 as an external control. If successful, this may provide patients with a treatment option that reduces overall disease burden by requiring less frequent infusions relative to eculizumab, while maintaining a comparable benefit/risk profile.

Detailed information about ravulizumab can be found in the Investigator's Brochure.

2.2. Background

2.2.1. Neuromyelitis Optica Spectrum Disorder

Neuromyelitis optica spectrum disorder is a severe disabling autoimmune inflammatory disorder of the CNS that predominately affects the optic nerves and spinal cord, and less commonly the brain. The disorder is ultra-rare, affecting 0.5 to 4.4 per 100,000 worldwide inhabitants (Pandit L, 2015).

The most common manifestations of NMOSD are characterized by recurrent, severe relapses of optic neuritis or transverse myelitis (TM), which result in a stepwise accumulation of relapse-related neurologic disability that can be irreversible (Wingerchuk DM, 2006). The annualized relapse rate (ARR) for patients with NMOSD is estimated to be about 1 relapse per year per

patient, with the vast majority of patients experiencing relapse (Flanagan EP, 2016; Ghezzi A, 2004; Jarius S, 2012).

In a study of AQP4-Ab positive neuromyelitis optica (NMO) patients, morbidity was significant with 18% experiencing permanent visual disability, 34% experiencing permanent motor disability, and 23% experiencing wheelchair dependency during the follow-up period (Kitley J, 2012).

2.2.2. Unmet Medical Need

SOLIRIS® (eculizumab), the first-in-class complement component C5 inhibitor, is the only therapy approved by the U.S. FDA for the treatment of NMOSD in adult patients who are anti-AQP4 Ab positive. Supportive treatments, including corticosteroids and other immunosuppressive therapies (ISTs), have been used based on clinical experience and consensus (Trebst C, 2014). Despite the use of ISTs as supportive therapy, a significant number of patients (> 50%) continued to experience disease relapses that resulted in incremental and permanent neurologic deficits and disability (Bichuetti DB, 2010; Jacob A, 2009).

Eculizumab has been demonstrated to be effective in reducing relapse risk. After the initial induction dose, eculizumab is administered every 2 weeks (q2w) to maintain adequate complement suppression. Neuromyelitis optica spectrum disorder is a chronic disease, and a frequent dosage regimen may impose a significant burden on patients, many of whom are disabled and require assistance with transportation.

Ravulizumab has a longer serum terminal elimination half-life and corresponding duration of pharmacologic activity relative to eculizumab. Ravulizumab was designed based on comprehensive modelling and simulation analyses to maintain efficacious concentrations across a longer dosing interval. The q8w dosage regimen is less burdensome for patients and has 4-fold fewer pharmacokinetic (PK) troughs, leading to fewer opportunities for achieving incomplete complement inhibition associated with sub-therapeutic exposure. The reduction in infusion frequency offers the potential to provide patients and physicians with an additional option for effective treatment of NMOSD while also improving quality of life (QoL) through fewer missed days of work, better treatment adherence, and improved accessibility.

2.2.3. Role of Complement Activation in NMOSD

Complement activation is a major determinant of disease pathogenesis in patients with NMOSD (Hinson SR, 2009; Nytrova, 2014; Papadopoulos MC, 2012; Verkman, 2012). Binding of AQP4 IgG to the AQP4 water channel, which is highly expressed on astrocytic surfaces in the CNS, has been shown to lead to hexameric assembly of immunoglobulin G (IgG). This in turn recruits and activates complement C1, the first step in activation of the complement cascade (Diebolder CA, 2014). Complement activation initiates an inflammatory cascade that induces permeabilization of the blood brain barrier and astrocyte necrosis. Lesions that form during this process are indicative of NMOSD and are positive for anti-AQP4 Abs and complement (Papadopoulos MC, 2012).

The therapeutic role of inhibition of terminal complement activation was demonstrated with eculizumab in Study ECU-NMO-301. Study ECU-NMO-301 was a randomized, double-blind, placebo-controlled, multicenter study that evaluated the safety and efficacy of eculizumab in patients with relapsing NMOSD. A significant effect on the time to first adjudicated On-trial

Relapse was observed for eculizumab compared with placebo (p<0.0001). An approximately 94.2% reduction in the risk of relapse was observed in patients who received eculizumab compared with placebo (Pittock SJ, 2019). In conjunction with the efficacy results, the serum free C5 results indicated that immediate, complete, and sustained terminal complement inhibition was achieved.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and expected adverse events (AEs) of ravulizumab may be found in the Investigator's Brochure.

2.3.1. Risk Assessment

Ravulizumab functions by blocking terminal complement; therefore, patients have increased susceptibility to serious infections, in particular, Neisseria meningitidis (*N meningitidis*). Specific risk mitigation measures in place are described in Section 8.1.4.

Based on the past human experience and cumulative clinical trial safety data of ravulizumab in PNH and atypical hemolytic uremic syndrome (aHUS), ravulizumab has been demonstrated to be well tolerated and safe, and exposure to ravulizumab in humans has not raised any unexpected safety concerns.

As with any humanized mAb, administration of ravulizumab may lead to the development of anti-drug antibodies (ADAs). Monitoring of immunogenicity is planned, as described in Section 8.9. Administration of any investigational product may result in infusion reactions. Management of potential infusion reactions is described in Section 10.14.

2.3.2. Benefit Assessment

Neuromyelitis optica spectrum disorder is a severe, disabling disease with relapses and cumulative disability occurring in more than 90% of cases (Wingerchuk DM, 2006). The efficacy and safety of eculizumab compared to placebo in the treatment of adult patients with anti-AQP4 Ab-positive NMOSD has been demonstrated in Study ECU-NMO-301, a multinational, double-blind, parallel-group Phase 3 time-to-event study, in which treatment with eculizumab reduced the risk of NMOSD relapse by 94.2% compared to placebo (p<0.0001) (Pittock SJ, 2019). Given the high homology and specificity to complement component C5 between ravulizumab and eculizumab, treatment with ravulizumab is expected to result in comparable reduction in the risk of relapses in adult NMOSD patients.

2.3.3. Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to patients participating in this study, the potential risks identified in association with ravulizumab are justified by the anticipated benefits that may be afforded to patients with NMOSD.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the effect of ravulizumab on adjudicated On-trial[a] Relapses in adult patients with NMOSD	• Time to first adjudicated On-trial Relapse and relapse risk reduction
Secondary	
• To evaluate the safety of ravulizumab in adult patients with NMOSD	• Incidence of treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), and TEAEs leading to study drug discontinuation
• To evaluate the effect of ravulizumab on adjudicated annualized relapse rate (ARR) in adult patients with NMOSD	• Adjudicated On-trial ARR
• To evaluate the effect of ravulizumab on disease-related disability in adult patients with NMOSD	• Clinically important worsening from baseline in expanded disability status scale (EDSS)
• To evaluate the effect of ravulizumab on QoL in adult patients with NMOSD	• Change from baseline in EuroQoL-5D (EQ-5D)
• To evaluate the effect of ravulizumab on neurologic function in adult patients with NMOSD	• Clinically important change from baseline in Hauser ambulation index (HAI)
• To characterize the PK of ravulizumab in adult patients with NMOSD	• Change in serum ravulizumab concentration over the study duration
• To characterize the pharmacodynamics (PD) of ravulizumab in adult patients with NMOSD	• Change in serum free C5 concentration over the study duration
• To characterize the immunogenicity of ravulizumab in adult patients with NMOSD	• Presence and titer of ADAs over the study duration
Exploratory	
• To evaluate the effect of ravulizumab on severity of adjudicated On-trial Relapse in adult patients with NMOSD	• Change from baseline in Optic Spinal Impairment Score (OSIS)
• To evaluate the effect of ravulizumab on neurologic function in adult patients with NMOSD	• Characterize the change from baseline in visual acuity, color vision, and confrontational visual fields
• To evaluate the effect of ravulizumab on QoL in adult patients with NMOSD	• Change from baseline in Short Form Health Survey (SF-36)
• To evaluate the safety of ravulizumab in adult patients with NMOSD	• Change from baseline in vital signs, electrocardiogram (ECG) parameters, and clinical laboratory assessments • Shifts from Baseline in Columbia-suicide severity rating scale (C-SSRS)
• To characterize biomarkers in adult patients with NMOSD	• Change from baseline in levels of biomarkers of complement dysregulation, neuroinflammation and neural injury • Blood and cerebrospinal fluid (CSF) NMO-Ig (AQP4 Ab) concentration

[a] On-trial Relapses refer to relapses as determined by the Treating Physician that occur during the study treatment period. All relapses will be adjudicated by a separate Adjudication Committee.

4. STUDY DESIGN

4.1. Overall Design

Study ALXN1210-NMO-307 is a Phase 3, external placebo-controlled, open-label, multicenter study to evaluate the efficacy and safety of ravulizumab in adult patients with NMOSD. Approximately 55 eligible adult patients with NMOSD from North America, Europe, and the Asia Pacific region will be enrolled into the study. Enrollment for each geographic region will be approximately 28% to 40% of the total population (Section 6.3).

There are 4 periods in this study: Screening Period, Primary Treatment Period, Long-Term Extension Period, and Safety Follow-up Period. Patients will be screened for eligibility for up to 6 weeks during the Screening Period. The end of the Primary Treatment Period will be triggered when either (1) 2 patients have had an adjudicated On-trial Relapse; or (2) all patients have completed, or discontinued prior to, the Week 26 Visit; whichever comes later. However, if 2 patients have not had an adjudicated On-trial Relapse by the time all patients have completed, or discontinued prior to, the Week 50 visit, the end of the Primary Treatment Period will be triggered at that time. Note that patients who complete the visits indicated above (Week 26 or Week 50) will remain on the study in the Primary Treatment Period until the Primary Treatment Period ends. For examples of different scenarios of the end of the Primary Treatment Period, please refer to Section 4.4. Based on the estimated enrollment rate, the duration of the Primary Treatment Period for each patient is expected to be between 26 weeks and approximately 2.5 years. The Primary Treatment Period ends and the Long-Term Extension Period starts when all patients have completed their End of Primary Treatment (EOPT) Visit within the timeframe specified in Section 4.4. All patients will continue to receive ravulizumab during the Long-Term Extension Period for up to approximately 2 years, or until ravulizumab is approved and/or available (in accordance with country-specific regulations), whichever occurs first. Based on the estimated enrollment rate of NMOSD patients, the total treatment duration for each patient will be up to approximately 4.5 years. After the last dose of study drug or early discontinuation (ED), patients will be followed for 8 weeks. The total study duration for each patient will be up to approximately 4.75 years.

4.2. Scientific Rationale for Study Design

The study has been designed to provide data that adequately characterize the benefit-risk profile of ravulizumab for the treatment of patients with NMOSD, using placebo data from Study ECU-NMO-301 as an external control.

4.2.1. External Placebo-Controlled, Open-Label Design

Study ECU-NMO-301 demonstrated the efficacy of eculizumab in reducing NMOSD relapses, with a 94.2% reduction in the risk of relapse as compared with placebo (Pittock SJ, 2019). As a derivative of eculizumab, ravulizumab targets an identical C5 motif to inhibit terminal complement activity and is expected to have a similar effect on relapses as that produced by eculizumab.

The recent approval of Soliris for NMOSD, the first approved therapy for NMOSD, is expected to change the treatment landscape and make it challenging to randomize patients to a placebo

group. However, it is important to employ a comparator group to provide adequate assessment of the safety and efficacy of ravulizumab.

A single-arm design, utilizing the placebo group from Study ECU-NMO-301 (conducted 2014 to 2018) as an external placebo control, allows for a robust assessment of ravulizumab as a treatment option for NMOSD. Whenever possible, in order to ensure a valid comparison, constancy will be maintained with Study ECU-NMO-301, including the inclusion of similar patient populations, permitted concomitant medications, adjudication procedures, and endpoints.

4.2.2. Rationale for the Selected Endpoints

4.2.2.1. Efficacy Endpoints

In NMOSD, the measurable, biological aspects include relapse and disability. Disability in NMOSD is a direct consequence of relapse, supporting the relevance of measuring relapses as the efficacy endpoint in Study ALXN1210-NMO-307.

In this study, the occurrence of relapses is evaluated using the primary endpoint time to first adjudicated On-trial Relapse and the secondary endpoint ARR. Time to first adjudicated On-trial Relapse provides useful information regarding the efficacy of ravulizumab. Since effectiveness of a treatment can be based on delaying and/or reducing the occurrence of relapses, a time to first relapse endpoint is an appropriate efficacy endpoint for prospectively designed studies in NMOSD (Weinshenker, 2015). The external placebo group from Study ECU-NMO-301 will be utilized as an appropriate control group given that the primary endpoint in that trial was also time to first adjudicated On-trial Relapse and the adjudication process and relapse definition will remain constant between the two trials.

Additionally, the effect of ravulizumab on the frequency of relapses will be measured using the Adjudicated On-trial ARR. A 95% confidence interval will be calculated around the ARR.

4.2.3. Rationale for the Duration of the Primary Treatment Period

In Study ALXN1210-NMO-307, the end of the Primary Treatment Period will be triggered when either (1) 2 patients have had an adjudicated On-trial Relapse; or (2) all patients have completed, or discontinued prior to, the Week 26 Visit; whichever comes later. However, if 2 patients have not had an adjudicated On-trial Relapse by the time all patients have completed, or discontinued prior to, the Week 50 visit, the end of the Primary Treatment Period will be triggered at that time. Note that patients who complete the visits indicated above (Week 26 or Week 50) will remain on the trial in the Primary Treatment Period until the Primary Treatment Period ends. Based on the estimated enrollment rate, the first patient enrolled will have been in the Primary Treatment Period for up to approximately 2.5 years, with the remaining patients having been in the Primary Treatment Period ranging between 26 weeks and up to approximately 2.5 years.

The cut-off of 26 weeks for the last patient was chosen for several reasons. In Study ECU-NMO-301, key observations could already be made by that time: 2 of the 3 adjudicated On-trial Relapses observed in the eculizumab group were observed, and 12 of 20 adjudicated On-trial Relapses had been observed in the placebo group. Given the similarities of ravulizumab and eculizumab, we expect to see a similar response in the first 26 weeks of treatment with ravulizumab. This design ensures that there will be limited number of patients censored during the first 26 weeks in the analysis of the time to first adjudicated On-trial

Relapse: in Study ECU-NMO-301, only 5 out of 143 (3.5%) patients had discontinued study treatment within the first 26 weeks (4 in the eculizumab arm and 1 in the placebo arm). It is also recognized that based on expected enrollment timelines, many of the patients will have been on treatment for more than 1 year by the time the last patient completes their Week 26 Visit, providing efficacy and safety data over time that allows for a robust comparison with data collected over a similar timeframe in the placebo group of Study ECU-NMO-301.

In the event that 2 patients have not experienced an adjudicated On-trial Relapse by the time the last patient has completed the Week 26 visit, all patients will remain in the Primary Treatment Period until 2 patients have experienced an adjudicated On-trial Relapse, or until the last patient has completed the Week 50 Visit. The criteria of the maximal additional follow-up time and the 2 adjudicated On-trial Relapses in 2 patients are chosen in part to more closely approximate the mean time on treatment (89.4 weeks) and the adjudicated On-trial ARR (0.02) of patients in the eculizumab arm of Study ECU-NMO-301. Furthermore, if the full additional 24 weeks of follow-up occur, this will ensure that all patients who do not discontinue pre-maturely will have a minimum of 50 weeks of follow-up.

4.2.4. Rationale for the Selected Patient Population

Complement activation is a major determinant of disease pathogenesis in patients with anti-AQP4 positive NMOSD (Nytrova, 2014). Inhibiting terminal complement activation with ravulizumab, therefore, represents a biologically rational approach for the treatment of patients with anti-AQP4 positive NMOSD. Study entry criteria were carefully selected to reflect an adult patient population consistent with the anti-AQP4 positive NMOSD population likely to be treated with ravulizumab in clinical practice.

4.3. Justification for Dose

4.3.1. Ravulizumab

Targeting complete terminal complement inhibition as a therapeutic strategy in the treatment of patients with NMOSD has been validated by data from the eculizumab clinical program. The dosing regimen of ravulizumab was designed to target immediate, complete, and sustained inhibition of terminal complement in patients. The weight-based doses of ravulizumab in the PNH program were premised on PK/PD data from early and late clinical development studies in healthy adult volunteers and patients with PNH. The proposed ravulizumab dosage regimen (Section 6.1; Section 8.1.6.1) is the approved regimen for the treatment of patients with PNH ULTOMIRIS® United States Prescribing Information (USPI), and the same dose regimen is also included in the initial marketing authorization application (MAA) in the EU. Therefore, the same dosage regimen is selected for this study. Additional PK/PD information supporting the selected dose regimen can be found in the current Investigator's Brochure (IB).

Patients may be switched from the 10 mg/mL to the 100 mg/mL formulation of ravulizumab with no change to the weight-based dose regimen during the Long-Term Extension Period. The 100 mg/mL IV formulation of ULTOMIRIS® (ravulizumab) is commercially approved in the United States, European Union, and Japan for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS). The 100 mg/mL ravulizumab is a higher concentration IV formulation which provides shorter preparation and

infusion times while delivering comparable PK, safety, and efficacy to the 10 mg/mL formulation of ravulizumab.

4.3.2. Supplemental Dose

Supplemental doses of ravulizumab (Section 8.1.6.2) may be administered to patients who receive plasma exchange (PE)/plasmapheresis (PP) (Section 6.5.1.3) or IVIg (Section 6.5.2) as acute therapy following an On-trial Relapse. The supplemental dose of ravulizumab has been selected based on PK simulations. Consistent with approved eculizumab labeling for treating adult and pediatric patients with aHUS, adult patients with generalized myasthenia gravis (gMG) and adult patients with NMOSD, supplemental dosing of ravulizumab in the amount of 50% (rounded up if not an integral of 300 mg due to vial configuration) will be given in the setting of concomitant PP/PE therapy.

4.4. End of Primary Treatment

The end of the Primary Treatment Period will be triggered when either (1) 2 patients have had an adjudicated On-trial Relapse; or (2) all patients have completed, or discontinued prior to, the Week 26 Visit; whichever comes later. However, if 2 patients have not had an adjudicated On-trial Relapse by the time all patients have completed, or discontinued prior to, the Week 50 visit, the end of the Primary Treatment Period will be triggered at that time. Note that patients who complete the visits indicated above (Week 26 or Week 50) will remain on the study in the Primary Treatment Period until the Primary Treatment Period ends.

The 3 ways that the Primary Treatment Period may end, given the above criteria, are as described in the following examples:

1. If 2 adjudicated On-trial Relapses have been observed by the time all patients have completed, or discontinued prior to, Week 26, the end of the Primary Treatment Period will be triggered.
2. If all patients have completed Week 26, or discontinued prior to Week 26, and 2 adjudicated On-trial Relapses have not yet been observed, but 2 adjudicated On-trial Relapses are then observed before all patients have completed, or discontinued prior to, Week 50, then the end of the Primary Treatment Period will be triggered when the second adjudicated On-trial Relapse has been adjudicated positively.
3. If 2 adjudicated On-trial Relapses have not been observed by the time all patients have completed Week 50, or discontinued prior to Week 50, then the end of the Primary Treatment Period would be triggered at that time.

If the EOPT Visit coincides with an upcoming scheduled study visit, patients will be required to complete all assessments for the EOPT Visit and can also be administered their scheduled dose of ravulizumab.

The end of the Primary Treatment Period is defined as the end of the 14-day window of the EOPT Visit.

4.5. End of Study Definition

A patient is considered to have completed the study by satisfying either one of the following conditions:

1. The patient has completed all phases of the study including the last visit shown in the Schedule of Activities.
2. The patient has completed the study early because ravulizumab has become registered or approved.

The end of the study is defined as the date of the last visit of the last patient (Section 1.3) in the trial globally.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Patients are eligible to be included in the study only if all of the following criteria apply:

Age

1. Patient must be 18 years of age or older, at the time of signing the informed consent.

Type of Patient and Disease Characteristics

2. Anti-AQP4 Ab-positive at screening and a diagnosis of NMOSD as defined by the 2015 international consensus diagnostic criteria (Wingerchuk, 2015). A historically positive anti-AQP4 Ab test may be acceptable if the test was performed using an acceptable, validated cell-based assay from an accredited laboratory. In this setting, the historical test result and related information need to be reviewed and approved by the Sponsor's Medical Monitor prior to initiating study treatment.
3. At least 1 attack or relapse in the last 12 months prior to the Screening Period
   NOTE: Patients with a single life-time attack will be considered to satisfy inclusion criterion #3 if the attack occurred in the last 12 months.
4. Expanded Disability Status Scale (EDSS) score ≤ 7
5. Patients who enter the trial receiving supportive IST (eg, corticosteroids, azathioprine [AZA], mycophenolate mofetil [MMF], methotrexate [MTX], and tacrolimus [TAC]) for the prevention of relapse, either in combination or monotherapy, must be on a stable dosing regimen of adequate duration prior to Screening with no plan to change the dose during the study period (defined as from the screening visit through the end of the study) as follows:
   a. If patients who enter the study are receiving AZA, they must have been on AZA for ≥ 6 months and have been on a stable dose for ≥ 2 months prior to Screening.
   b. If patients who enter the study are receiving other ISTs (eg, MMF, MTX, or TAC), they must have been on the IST for ≥ 3 months and have been on a stable dose for ≥ 4 weeks prior to Screening.
   c. If patients who enter the study are receiving oral corticosteroids, they must have been on a stable dose for ≥ 4 weeks prior to Screening.
   d. If a patient enters the trial receiving oral corticosteroid(s) with or without other IST(s), the daily corticosteroid dose must be no more than prednisone 20 mg/day (or equivalent) prior to Screening.
6. Vaccinated against *N. meningitidis* within 3 years prior to, or at the time of, initiating ravulizumab. Patients who initiate study drug treatment less than 2 weeks after receiving a meningococcal vaccine must receive appropriate prophylactic antibiotics until 2 weeks after the vaccination.

Weight

7. Body weight ≥ 40 kg

Sex

8. Male or female

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a. Male patients:

Male patients must agree to use contraception as detailed in the protocol (Section 10.4) during the treatment period and for at least 8 months after last dose of study drug and refrain from donating sperm during this period.

b. Female patients:

A female patient is eligible to participate if she is not pregnant, not breastfeeding, and at least 1 of the following conditions applies:

- Not a woman of childbearing potential (WOCBP)

OR

- Is a WOCBP and using a highly effective or acceptable contraceptive method as described in Section 10.4 during the treatment period and for a minimum of 8 months after the last dose of study drug.
  - The Investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study drug. A WOCBP must have a negative serum pregnancy test at screening and a negative urine pregnancy test before the first dose of study drug. Additional requirements for pregnancy testing during and after study drug are described in Section 10.4. The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

9. Capable of giving signed informed consent as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol

5.2. Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

Medical Conditions

1. History of *N. meningitidis* infection.
2. Human immunodeficiency virus (HIV) infection (evidenced by HIV-1 or HIV-2 antibody titer)
3. History of unexplained infections
4. Active systemic bacterial, viral, or fungal infection within 14 days prior to study drug administration on Day 1

5. Presence of fever ≥ 38°C (100.4°F) within 7 days prior to study drug administration on Day 1
6. Hypersensitivity to murine proteins or to 1 of the excipients of ravulizumab
7. Any medical condition that, in the opinion of the Investigator, might interfere with the patient's participation in the trial, poses any added risk for the patient, or confounds the assessment of the patient

Prior/Concomitant Therapy

8. Previously or currently treated with a complement inhibitor.
9. Use of rituximab within 3 months prior to Screening
10. Use of mitoxantrone within 3 months prior to Screening
11. Use of Intravenous Immunoglobulin (IVIg) within 3 weeks prior to Screening

Prior/Concurrent Clinical Study Experience

12. Participation in any other investigational drug study or exposure to an investigational drug or device within 30 days of Screening or 5 half-lives of the investigational drug, whichever is greater

Other Exclusions

13. Pregnant, breastfeeding, or intending to conceive during the course of the study
14. Patient is currently treated with a biologic medication that may affect immune system functioning, or has stopped treatment with a biologic medication that may affect immune system functioning, and 5 half-lives of the medication have not elapsed by the time of the Screening visit, unless otherwise specified in the protocol.
15. Participation in the PREVENT study (ECU-NMO-301), regardless of the study drug received (eculizumab or placebo)

5.3. Lifestyle Considerations

There is no lifestyle restriction for this study.

5.4. Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently treated with study drug.

Individuals who do not meet the criteria for participation in this study (screen failure) due to a reason that is expected to resolve or has resolved, may be rescreened based on discussion and agreement between the Investigator and the Medical Monitor.

A patient who experiences a relapse that meets the protocol definition of an On-trial Relapse (Section 8.2.3.2) during the Screening Period will be considered a screening failure. Such patients may be rescreened for enrollment into the trial after receiving treatment for the relapse and when, in the opinion of the Investigator and the Medical Monitor, the patient is medically

stable (Section 5.1; Section 5.2). The patient must meet the enrollment criteria at re-screening in order to enter the study.

6. STUDY DRUG

Study drug is defined as any study drug(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study patient according to the study protocol.

6.1. Study Drug(s) Administered

In this study, patients will receive open-label ravulizumab during the entire treatment period (Table 6). Detailed description of the study drug is provided in the Pharmacy Manual.

Refer to Section 8.1.6 for study drug dosage and administration and Section 1.3 SoA for dosing schedules.

Table 6 Study Drugs

Study drug name	Ravulizumab 10 mg/mL, 30 mL vial	Ravulizumab 100 mg/mL, 11 mL vial
Type	Biologic	Biologic
Dose formulation	Concentrated sterile, preservative-free solution with a concentration of (10 mg/mL) in single-use 30 mL vials, 30 mL extractable volume	Concentrated sterile, preservative-free aqueous solution (100 mg/mL) in single-use 11 mL vials, 11 mL extractable volume
Physical description	Clear to translucent, slight whitish color, practically free from particles	Liquid solution practically free from particles
Unit dose strength(s)	300 mg (10 mg/mL concentrated solution)	1100 mg (100 mg/mL concentrated solution)
Dosage level(s)[1]	Weight-based dose, starting 2 weeks after the initial loading dose, then maintenance dose q8w	Weight-based maintenance dose
Route of administration	IV infusion	IV infusion
Use	Experimental	Experimental
IMP and NIMP	IMP	IMP
Sourcing	Supplies provided by Alexion	Supplies provided by Alexion
Packaging and labeling	The solution is packaged in a 30 mL single-use vial with an extractable volume of 30 mL and a grey rubber stopper and with an aluminum overseal and a flip-off cap. Study drug will be supplied in kits and labeled as required per country requirement.	Glass vials and stoppered with a butyl rubber stopper with an aluminum overseal and a flip-off cap. Study drug will be supplied in kits and labeled as required per country requirement.

[1] Detailed information of study drug dose administration is provided in Section 8.1.6.
Abbreviations: IMP = investigational medicinal product; IV = intravenous; NIMP = non-investigational medicinal product; q8w = once every 8 weeks

6.2. Preparation/Handling/Storage/Accountability

Upon arrival of the study drug at the study site, the study drug kits should be removed from the shipping container and stored in their original cartons under refrigerated conditions at 2°C to 8°C (35°F to 47°F) and protected from light. Ravulizumab should not be frozen.

Study drug must be stored in a secure, limited-access storage area with temperature monitored daily.

Infusions of study drug should be prepared using aseptic technique. Ravulizumab will be further diluted in a 1:1 ratio with compatible diluent. Ravulizumab will be filtered with a 0.2 micron filter during infusion.

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drug received and any discrepancies are reported and resolved before use of the study drug.
2. Only patients enrolled in the study may receive study drug and only authorized site staff may supply or administer study drug. All study drug must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study drugs are provided in the Pharmacy Manual.

For detailed instruction on study drug preparation, handling, storage, and accountability, refer to the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is a single-arm, open-label study. All study patients, site personnel, Sponsor staff, Sponsor designees, and all staff directly associated with the conduct of the trial will be unblinded to patient treatment assignments.

To minimize potential for bias in this open-label study, operational measures will be employed regarding the efficacy endpoints and adjudication process. The trial database will be monitored according to prespecified guidelines in order to confirm that all potential relapses are collected and analyzed. An independent Relapse Adjudication Committee will evaluate each On-trial Relapse and confirm whether it meets the protocol defined criteria for an NMOSD relapse (Section 8.2.3.2). Additionally, while the EDSS Raters will be aware that all patients are on ravulizumab, the EDSS Raters will be blinded to all trial data when making their assessments.

The external control will be the placebo arm of Study ECU-NMO-301, a randomized double-blind study conducted from 2014 to 2018, and upon which this study is based. The design is similar in most aspects: the inclusion criteria are the same in most cases, with modifications that include using the most recently updated NMOSD diagnostic criteria and updated historical relapse rate parameters. To minimize any biases arising from slight differences in study designs and unforeseen enrollment differences, statistical analyses will include covariate adjustment techniques as warranted.

Enrollment for each geographic region will be approximately 28% to 40% of the total population. This will allow for relative maintenance of constancy from a regional standpoint between the ALXN1210-NMO-307 and the ECU-NMO-301 study populations.

6.4. Study Drug Compliance

The infusion of study drug into patients will be under the supervision of the Investigator or their designee to ensure that the patients receive the appropriate dose at the appropriate timepoints during the study.

The date and time of each dose administered will be recorded in the source documents and recorded in the case report form (CRF).

6.5. Concomitant Therapy

Any medication (including over-the-counter or prescription medicines, vitamins, minerals, and/or herbal supplements) or vaccine that the patient is receiving at the time of enrollment or receives during the study must be recorded in the patient's source document/medical chart and electronic case report form (eCRF) along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Any changes in concomitant medications also will be recorded in the patient's source document/medical chart and eCRF. When possible, concomitant medications will be recorded from the first infusion of ravulizumab until the patient has discontinued or completed the study.

Information regarding the use of ISTs including steroids must be collected. Meningococcal vaccination and antibiotics administered for prophylaxis of meningococcal infection (if applicable) will also be recorded.

Any concomitant medication deemed necessary for the patient's care during the study, or for the treatment of any AE, along with any other medications, other than those listed as disallowed medications in Section 6.5.2, may be given at the discretion of the Investigator. However, it is the responsibility of the Investigator to ensure that details regarding all medications are recorded in full in the patient's source document/medical chart and eCRF.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1. Allowed Medications and Therapies

The following concomitant medications and therapies are allowed in this study.

6.5.1.1. Palliative and Supportive Care

Palliative and supportive care is permitted during the course of the trial for underlying conditions.

6.5.1.2. Immunosuppressive Agents

The supportive immunosuppressive therapies (ISTs) for relapse prevention, either in combination or monotherapy, are permitted at the discretion of the Investigator, such as:

- corticosteroids
- azathioprine (AZA)
- mycophenolate mofetil (MMF)
- methotrexate (MTX)

- tacrolimus (TAC)
- cyclosporine
- cyclophosphamide

If a patient receives supportive ISTs prior to the study and continues to receive stable maintenance therapy during the study, refer to inclusion criteria (Section 5.1) for the requirements on ISTs to ensure that the patient is on a stable dose within limits required for this study as described in study criteria (Section 5).

For each patient, no adjustment in IST dosage and no new ISTs will be permitted for the first 106 weeks, unless the patient experiences a relapse or a safety event, and a change in IST dose or regimen is deemed necessary by the Investigator to guarantee the patient's safety.

Any changes in immunosuppressive therapy will be recorded in the source documents and eCRF page for concomitant medication.

6.5.1.3. Standardized Treatment for Relapse

The treatment of relapse is at the discretion of the Treating Physician. While the exact treatment for a potential relapse is ultimately at the discretion of the Investigator, the following standardized treatment regimen for a confirmed On-trial Relapse (Section 8.2.3.2) is recommended, in accordance with expert opinion:

One gram (1 g) intravenous methylprednisolone (IVMP) administered daily for 3-5 days followed by oral prednisone tapering.

- If the patient improves, then continue the trial assessments as per schedule of this protocol.
- If there is no or minimal response to IVMP, or if the Investigator determines that PE/PP is the appropriate initial option, PE/ PP will be allowed at the discretion of the treating neurologist. Five cycles of PE, each removing 1.0 to 1.5 volumes of circulating plasma, are recommended for treatment of attacks that do not respond to IVMP.
    - If a patient undergoes PE/PP for an On-trial Relapse during the Treatment Period, a supplemental dose of study drug should be administered after each PE/PP as described under Supplemental Dose in Section 8.1.6.2. After receiving the supplemental dose, the patient will continue on the protocol-specified dosing schedule in the SoA (Section 1.3).

6.5.2. Disallowed Medications and Therapies

The following medications and therapies are prohibited during the study.

- Mitoxantrone
- Rituximab or other biologics that may affect immune system functioning (eg, tocilizumab, ocrelizumab, satralizumab, or inebilizumab)
- Immunomodulatory therapies, including interferon beta-1b; interferon beta-1a, glatiramer acetate, natalizumab, alemtuzumab, dimethyl fumarate, teriflunomide, siponimod, and fingolimod.

- IVIg or subcutaneous Ig used as maintenance therapy
- Note: IVIg used acutely for relapse treatment is allowed.
- PE for relapse prevention
- Bruton tyrosine kinase (BTK) inhibitors

6.6. Dose Modification

Dose modification is not permitted for this study.

6.7. Intervention after the End of the Study

Ravulizumab will not be provided to the patients after the last scheduled dosing (Section 1.3). All patients will be followed for safety for an additional 8 weeks after the last dose of study drug or early discontinuation.

7. DISCONTINUATION OF STUDY DRUG AND PATIENT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Drug

In rare instances, it may be necessary for a patient to permanently discontinue (definitive discontinuation) study drug. If study drug is definitively discontinued, the patient should remain in the study to be evaluated for the 8-week safety follow up visit. See the SoA for data to be collected at the time of discontinuation of study drug and follow-up and for any further evaluations that need to be completed.

Patients will be discontinued from study drug if any of the following occur during the study:

1. Serious hypersensitivity reaction;
2. Severe uncontrolled infection;
3. Use of disallowed medication as defined in Section 6.5.2;
4. Pregnancy or planned pregnancy; or
5. Sponsor or the Investigator deems it is necessary for the patient.

See the SoA (Section 1.3) for data to be collected at the time of study drug discontinuation and follow-up and for any further evaluations that need to be completed.

7.2. Patient Discontinuation/Withdrawal from the Study

All efforts should be made to ensure patients are willing to comply with study participation prior to conducting the screening procedures. The study staff should notify the Sponsor and their site monitor of all trial withdrawals as soon as possible. The reason for patient discontinuation must be recorded in the source documents and eCRF.

- A patient may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral compliance, or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Section 1.3). Patients who discontinue early should be followed for safety for an additional 8 weeks and for any further evaluations that need to be completed.
- The patient will be permanently discontinued both from the study drug and from the study at that time.
- If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

7.3. Lost to Follow-up

If a patient fails to return, or is otherwise unavailable, for a scheduled visit within the acceptable visit window (Section 1.3), the site study staff must make a reasonable attempt to contact the patient to determine the reason for missing the appointment.

Patients who fail to return for a scheduled visit must be contacted by the site's study staff to determine the reason for missing the appointment. As it is vital to obtain any patient's missing visit information to ensure the missed appointment was not due to an AE or potential relapse, every effort must be made to undertake protocol-specified safety follow-up procedures.

In the exceptional circumstance where a patient cannot or does not come to the study site for examination, the patient will be instructed to see his or her local neurologist or physician. In this event, if possible, the Treating Physician or designee will contact the local neurologist or physician to obtain as much information as possible about the patient's medical and neurological condition, and provide clinical guidance, if needed. The study site will obtain relevant medical records as documentation from the local physician's examination and enter relevant data in the Relapse Evaluation Visit form or in the AE form as appropriate.

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered as lost to follow up.

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.8.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the patient should receive study drug.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the patient's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1. General Assessments and Procedures

8.1.1. Informed Consent

The Investigator or qualified designee must obtain a signed and dated informed consent form from each patient prior to conducting any study procedures. All efforts should be made to ensure patients are willing to comply with trial participation prior to conducting the screening procedures.

8.1.2. Treating Physician

The Treating Physician is the Principal Investigator (PI) /Sub-Investigator for the study who will be responsible for the overall patient management including patient eligibility evaluation, supervision of the study drug administration, recording and treating of AEs and monitoring of safety assessments.

At the time of a relapse, the Treating Physician will perform a complete neurologic examination and determine if the patient's symptoms and signs meet the criteria for an On-trial Relapse (Section 8.2.3.2). They may also treat the patient's relapse according to the recommended On-trial Relapse Treatment regimen. Ultimately, treatment and treatment options for On-trial Relapse as well as any changes in the ISTs following an On-trial Relapse are at the discretion of the Treating Physician.

8.1.3. Medical History and NMOSD History

The Investigator will review the patient's history and diagnosis and document the following at the Screening Visit:

- Medical history including all relevant medical/surgical history

- NMOSD diagnosis date as well as prior Magnetic Resonance Imaging (MRIs) that contributed to the diagnosis. Confirmation of the NMOSD diagnosis as defined by the International Panel for NMO Diagnosis (IPND) criteria (Section 10.5), including the specific criteria the patient met for the diagnosis. Only patients who are both anti AQP4 Ab-positive and otherwise meet the 2015 IPND criteria will be eligible for participation.
- Information about relapses which occurred before screening and that meet the protocol definition of Historical Relapse (Section 8.2.3.1) will be recorded. For relapses that occurred in the last 24 months, this information will include the following
    - The number of relapses (onset dates)
    - The clinical presentation of each relapse (eg, optic neuritis [ON], TM, brainstem, area postrema, or other)
    - Acute and maintenance treatments and dosing regimens

8.1.4. Vaccine and Antibiotic Prophylaxis

As with any terminal complement antagonist, the use of ravulizumab increases the patient's susceptibility to meningococcal infection (*N meningitidis*). To reduce the risk of meningococcal infection, all patients must be vaccinated against meningococcal infections within the 3 years before or at the time of initiating study drug.

- Patients who initiate study drug less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination.
- Patients must be vaccinated or revaccinated according to current national vaccination guidelines or local practice for vaccination use with complement inhibitors (eg, eculizumab, ravulizumab).
- Vaccines against serotypes A, C, Y, W135, and B, where available, are recommended to prevent common pathogenic meningococcal serotypes.
- Vaccination may not be sufficient to prevent meningococcal infection. Consideration should be given per official guidance and local practice on the appropriate use of antibacterial agents.
- All patients should be monitored for early signs of meningococcal infection, evaluated immediately if infection is suspected, and treated with appropriate antibiotics, if necessary.

8.1.5. Inclusion/Exclusion Criteria

All inclusion (Section 5.1) and exclusion (Section 5.2) criteria must be reviewed by the Investigator or qualified designee to ensure the patient qualifies for study participation.

Both the Investigator and the Sponsor must approve patient eligibility before enrollment.

8.1.6. Study Drug Administration

This section describes the dosage regimen of study drugs. At the scheduled dosing visits (Section 1.3), study drug administration should be performed after all other tests and procedures have been completed, excluding the postdose blood sampling for PK and free C5.

Refer to Section 6 for additional information on study drugs including preparation, handling, storage, and accountability. For detailed instructions, refer to the Pharmacy Manual.

8.1.6.1. Ravulizumab

Patients will receive a weight-based loading dose of ravulizumab via IV infusion on Day 1, followed by a weight-based maintenance dose on Day 15 (Table 7), then once every 8 weeks (q8w) thereafter (Table 7). The entire treatment duration is up to approximately 4.5 years, when all patients complete the 2-year Long-Term Extension Period or until ravulizumab is approved and/or available (in accordance with country-specific regulations), whichever occurs first. Patients may be switched from the 10 mg/mL to the 100 mg/mL formulation of ravulizumab with no change to the weight-based dose regimen during the Long-Term Extension Period.

Table 7: Weight-based Doses of Ravulizumab

	Body Weight (kg)[a]	Dose (mg)
Loading dose	≥ 40 to < 60	2400
	≥ 60 to < 100	2700
	≥ 100	3000
Maintenance dose	≥ 40 to < 60	3000
	≥ 60 to < 100	3300
	≥ 100	3600

[a] Dose regimen will be based on the last recorded study visit body weight. This will commonly be the current visit as weight will be measured prior to dose preparation on the day of the visit. If the study drug is prepared the night before a visit, the weight from the most recent prior study visit should be used.

Depending on when a relapse occurs, ravulizumab scheduled dosing visits may or may not overlap with the Relapse Evaluation Visit and/or Follow-Up Relapse Evaluation Visits. Ravulizumab dosing should continue as scheduled during the Relapse Evaluation Period.

8.1.6.2. Supplemental Dose

During the study, PE/PP or IVIg will be allowed at the discretion of the Treating Physician for On-trial Relapse (Section 6.5.1.3).

- If PE/PP is administered on a non-dosing visit as specified in the SoA (Section 1.3), a supplemental dose will be administered within 4 hours after each session of PE/PP is completed, and will be based on the most recently administered ravulizumab dose (Table 8).
- If PE/PP is administered on a scheduled dosing visit as specified in the SoA (Section 1.3), a ravulizumab supplemental dose will not be administered. Patients will receive their regular dose of ravulizumab (Section 8.1.6.1) 60-120 minutes after that session of PE/PP is completed.

- It is noted that PE/PP is typically administered in multiple sessions over the course of 1-2 weeks. If one session occurs on the day of a scheduled dosing visit, then the regular dose of ravulizumab is administered on that day. However, for the other sessions in the same 1-2 week course that do not occur on the scheduled dosing visit day, only the supplemental dose will be given.
- If IVIg is administered, ravulizumab supplemental dosing is only required after the last dose of IVIg in the series.
  - If the last dose of IVIg in the series is given on a non-dosing visit as specified in the SoA (Section 1.3), a supplemental dose of 600 mg ravulizumab will be administered within 4 hours after the completion of the IVIg infusion.
  - If the last dose of IVIg in the series is administered on the same day as a scheduled dosing visit as specified in the SoA (Section 1.3), then a ravulizumab supplemental dose will not be administered, and patients will receive their regular dose of ravulizumab (Section 8.1.6.1) 60-120 minutes after the completion of the IVIg infusion.

Refer to Section 8.6.2 for PK and free C5 sample collection during On-trial Relapse.

After receiving the supplemental dose, patients are to continue study drug infusion according to the protocol-specified dosing schedule (Section 1.3).

Table 8: Supplemental Dose of Ravulizumab Administered at Nonscheduled Dosing Visits After PE/PP Treatment for On-trial Relapse

Dose Name	Most Recently Scheduled Dose	Supplemental Dose (mg)
Loading dose	2400	1200
	2700	1500
	3000	1500
Maintenance dose	3000	1500
	3300	1800
	3600	1800

8.1.7. Visits at Home or Alternative Healthcare Facilities

Patients may have an opportunity to receive study drug administration remotely at a medical facility that is located near the patient's home or at the patient's home with the permission of the Investigator in accordance with all national, state, and local laws or regulations of the pertinent regulatory authorities. Home infusions may be considered only for patients who have tolerated previous drug infusions well, without clinically significant infusion reactions, at the study site.

Remote visit options may be at the Investigator's discretion and oversight, in accordance with the local regulations, and conducted by a qualified medical professional. Information about AEs, concomitant medications, and NMO signs or symptomatology must be sent to the Investigator's site for evaluation on the day of the remote visit. In case of any signs or symptoms indicating an SAE or a potential relapse, the patient will need to be evaluated at the study site.

Monitoring, treatment, and management of infusion reactions for patients receiving drug infusions at home are described in detail in the Nursing Instruction Manual and Section 10.14.

8.2. Efficacy Assessments

8.2.1. Neurologic Examination

A complete general neurologic examination will be performed at the scheduled visits (Section 1.3) by the Treating Physician (Section 8.1.2) who is a study Investigator and has been properly trained as clinical evaluator, preferably the same Treating Physician, throughout the study.

The complete general neurologic examination includes assessments of the following systems: mental status, fundus examination, cranial nerves, deep tendon reflexes, plantar responses, power/strength, sensation, coordination, and gait/balance.

8.2.2. NMO Symptom Card and Evaluation

Before receiving the first dose of study drug at the Day 1 Visit, patients are given an NMO Symptom Card, which lists potential signs and symptoms of NMOSD relapse and contact information.

At each visit throughout the study, study staff should ensure that the patient has the NMO Symptom Card. The Treating Physician will review and assess the patient for any signs or symptoms indicative of relapse.

To minimize the risk of non-reporting or delayed reporting of a relapse when a patient is experiencing relapse symptoms, biweekly phone call visits will be implemented by study sites between the scheduled dosing visits (Section 1.3). A phone visit at Week 6, a scheduled non-dosing visit, will not be necessary. At each phone visit, patients will be queried about safety and any neurologic symptoms suggestive of a relapse that are ongoing or that have occurred since the last visit. If a potential relapse is identified, the patient will be asked to have an onsite relapse evaluation visit to determine whether this patient's symptomatology meets the protocol defined criteria for relapse.

8.2.3. Relapse

8.2.3.1. Historical Relapse

Historical relapses are the relapses that occurred before the Screening Visit, including the first NMOSD attack. For this protocol, historical relapse is defined as a new onset of neurologic symptoms or worsening of existing neurologic symptoms with an objective change on neurologic examination (clinical findings or MRI findings, or both) that persisted for more than 24 hours and/or the new onset of neurologic symptoms or worsening of existing neurologic symptoms that required treatment. Treatment is defined as use of high-dose IV steroids, PE/PP or IVIg. Events that occur within a 30-day interval are considered as one relapse.

8.2.3.2. On-trial Relapse

8.2.3.2.1. Definition of On-trial Relapse

On-trial Relapses are acute attacks that occur during the study treatment period. For this protocol, On-trial Relapse is defined as a new onset of neurologic symptoms or worsening of existing neurologic symptoms with an objective change (clinical sign) on neurologic examination that persists for more than 24 hours as confirmed by the Treating Physician (Section 8.1.2). The signs and symptoms must be attributed to NMOSD, ie, not caused by an identifiable cause such as infection, excessive exercise, or excessively high ambient temperature. Isolated changes on MRI or other imaging investigation with no related clinical findings are not considered an On-trial Relapse.

8.2.3.2.2. Evaluation of On-trial Relapse

On-trial Relapses will be monitored throughout the study. The Investigator or a qualified designee will review the signs and symptoms of a potential relapse with the patient in detail at each visit.

Patients will be educated on the potential signs and symptoms of NMOSD relapse and will be instructed to contact the study site at the first sign or symptom of a potential relapse.

Patients should be evaluated within 24 hours (and no later than 48 hours) of notification of signs or symptoms suggestive of a potential relapse.

Evaluation of On-trial Relapses includes the following:

- Complete neurological examination to determine whether the clinical signs, symptoms and examination findings meet the definition of an On-trial Relapse
- Assessment of relapse severity based on the OSIS (Section 8.2.9; Section 10.10). The OSIS Visual Acuity (VA) Subscale Scores will be used to categorize the severity of ON. The OSIS Motor Subscale Scores and Sensory Subscale Scores will be used to categorize the severity of TM.
- Evaluation of the neurological functional systems based on the Kurtzke's Functional System Scores (FSS) and the disability level based on the EDSS score (Section 8.2.5).
- Ambulatory function assessment using the HAI (Section 8.2.8).
- Ophthalmological examination including VA, confrontational visual fields (VF), and color vision (Section 8.2.10).
- MRI +/- gadolinium and/or optical coherence tomography (OCT) examinations should be performed to evaluate a potential relapse as determined by the Investigator (Section 8.2.11).
- Additional tests and the follow-up evaluation as specified in the SoA (Section 1.3).

8.2.3.2.3. Treatment for On-trial Relapse

At the time of a suspected relapse, the Treating Physician (Section 8.1.2) will perform a complete neurologic examination to determine if a patient is experiencing an On-trial Relapse. If

the event is determined as an On-trial Relapse by the Treating Physician, treatment for relapse, as well as any changes in the ISTs following relapse, are at the discretion of the Investigator.

The recommended standardized treatment for On-trial Relapse is provided in Section 6.5.1.

Refer to Section 8.1.6 for administration of ravulizumab supplemental dose during an On-trial Relapse.

8.2.3.2.4. On-trial Relapse Follow-up

Relapse Evaluation Visits to monitor the course of the relapse will be performed according to the schedule specified in the SoA (Section 1.3). Additional (unscheduled) Follow-up Relapse Evaluation Visits outside the specified time points will be made at the discretion of the Investigator or the sub-Investigator.

Following a relapse, a patient may continue in the trial if the patient and the Investigator/sub-Investigator decide that it is appropriate to continue to receive study drug.

All reports of possible relapses and actions taken for the possible relapse must be documented in the patient's source documents and recorded in the eCRF.

8.2.3.2.5. Adjudication of On-trial Relapse

On-trial Relapses will be independently reviewed by the Relapse Adjudication Committee (RAC), which consists of physicians who have particular expertise in NMOSD and will conduct independent reviews of all On-trial Relapses. The Committee will decide by majority vote whether each reported On-trial Relapse meets the objective criteria for an On-trial Relapse. A separate Charter will document all adjudication criteria and procedures for this study.

8.2.4. Case of Interest

Accurate identification of potential relapses is crucial for the scientific integrity of the study. In order to achieve this, the database will be analyzed for potential events (Cases of Interest) that were not reported by the Treating Physician as a relapse.

A Case of Interest is an event judged by the Treating Physician to **not** be an On-trial Relapse (ie, it is not an Investigator confirmed On-trial Relapse), but which meets the following criteria to be considered a Case of Interest and submitted to the RAC for adjudication:

- Patients who were seen by the Treating Physician for a 24- to 48-hour relapse evaluation visit and where the Treating Physician concluded that an On-trial Relapse did not occur, OR
- A sentinel AE (eg, AEs of weakness, sensory changes, especially in a dermatomal distribution, characteristic visual changes of NMOSD, or pseudo exacerbation of NMOSD) AND either:
    - An MRI was performed contemporaneously OR
    - Neurological symptoms were treated (by hospitalization or IVMP) OR
    - Contemporaneous objective worsening of the Treating Physician's Neurologic Examination (defined by answer of "worse" to clinically meaningful change question).

***Note**: a Case of Interest is also referred to as a 'pseudo relapse'. The terms may be used interchangeably.*

Refer to Section 10.15 for additional description of the Case of Interest identification process.

8.2.5. Expanded Disability Status Scale (EDSS)

The 10-point Neurostatus EDSS (modified Kurtzke EDSS), described in Section 10.6, is widely used and accepted as a valid tool for quantifying disability and monitoring changes in disability over time (Kurtzke, 1983).

The EDSS scale ranges from 0 to 10.0 in 0.5 unit increments.

8.2.5.1. Expanded Disability Status Scale

The total EDSS score is determined by 2 factors: gait and FSS (Section 8.2.5.2).

- EDSS scores below 4.0 are determined by the FSS alone.
- People with EDSS scores of 4.5 and above may have some degree of gait impairment.
- EDSS scores between 4.5 and 9.5 are determined by both gait abilities and the FSS.

8.2.5.2. Functional Systems Scores

A functional system (FS) represents a network of neuronal systems responsible for particular tasks/functions. The EDSS assigns a severity score to the patient's clinical status using FSS that evaluate dysfunction in the following 7 FSs (Section 10.6).

The FS of functional systems 1 through 7 are scored on a scale of 0 (low level of problems) to 5 or 6 (high level of problems) to best reflect the level of disability observed clinically.

8.2.5.3. EDSS and FSS Rater

The EDSS and FSS should be administered in person by a trained rater. The EDSS Rater will perform a complete Kurtzke neurologic examination and document the FSS and the EDSS score.

- The EDSS Rater shall not be the PI and cannot be directly involved in the trial patient's management. When possible, the EDSS Rater should be a physician. If a non-physician EDSS Rater (eg, specialized nurse) will be used, the rater must be approved by the Sponsor before performing the assessments.
- The EDSS Rater must remain blinded to all other study data as well as all other patient clinical data.
- The blinded EDSS Rater will be responsible for performing the EDSS assessments throughout the study including at the time of a relapse. When possible, the same blinded rater should perform the EDSS for each patient at visits specified in the SoA.
- The EDSS Rater will perform a complete Kurtzke neurologic examination, as described in Section 10.6 and document the Functional Systems Scores (FSS) and the EDSS score (Kurtzke, 1983).

For specific requirements for EDSS Rater qualification, refer to the training materials provided by the Sponsor.

Refer to Table 9 for the roles and responsibilities of Investigator and EDSS Rater.

Table 9: Roles and Responsibilities of the Treating Physician and EDSS Rater

Treating Physician	EDSS Rater
At protocol-specified timepoints: • Determine patient eligibility for the study • Overall patient management during the study, including study drug administration and safety assessments.	**At protocol-specified timepoints:** • Kurtzke neurologic assessment • Document FSS • Record EDSS score
At the time of relapse: • Initial patient assessment • Have the EDSS Rater record FSS and EDSS score[a] • Perform a complete neurologic examination • Determine if the patient has experienced an On-trial Relapse • Determine relapse severity by OSIS • Assess VA[a], confrontational visual fields, and color vision[a] • Assess ambulation by HAI[a] • Have the patient complete the EQ-5D and SF-36 • Treat relapse	**At the time of relapse:** • Perform the Kurtzke neurologic assessment • Document FSS • Record EDSS score
EDSS = Expanded Disability Status Scale; EQ-5D = Euro Quality of life-5 Dimensions; FSS = functional systems score; HAI = Hauser ambulation index; OSIS = Optic spinal impairment score; SF-36=short form health survey; VA = visual acuity. [a] Can be performed by the Investigator or a designee	

8.2.6. EuroQoL 5 Dimensions (EQ-5D)

The Euro Quality of Life (EQ-5D) (Section 10.7) is a self-assessed, standardized instrument to measure health-related QoL, which has been used in a wide range of health conditions, including NMOSD (Schrag, 2000). The EQ-5D consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS) (Section 10.7). EQ-5D should be administered prior to other study procedures at each visit. For patients who are blind, the script for face-to-face interview administration version of EQ-5D will be used (Section 10.7).

8.2.6.1. EQ-5D Descriptive System

The descriptive system is a 5-component scale including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each level is rated on a scale that describes the degree of problems in that area.

8.2.6.2. EQ Visual Analogue Scale

The EQ-5D VAS is an overall health state scale where the patient selects a number between 0 to 100 to describe the condition of their health, with 100 being 'The best health state you can imagine' and 0 being 'The worst health state you can imagine'.

This information can be used as a quantitative measure of health outcome as judged by the individual respondents. Previously published studies by EuroQol Group members showed preliminary evidence of the instrument's feasibility, reliability and validity.

8.2.7. Short Form Health Survey (SF-36)

The SF-36 is a 36-item self-report of health-related quality of life (Stewart, 1988; Ware, 1992). It contains 8 subscales measuring different domains of health-related quality of life: physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, vitality, social functioning, role-limitations due to emotional problems, and mental health. The two summary scores are the physical component summary and the mental component summary. There is no single overall score for the SF-36.

8.2.8. Hauser Ambulation Index (HAI)

The HAI (Hauser, 1983) is a rating scale developed to assess mobility by evaluating the time and degree of assistance required to walk 25 feet (Section 10.9).

The Treating Physician or an appropriately trained designee will perform the HAI test at the protocol specified visits (Section 1.3).

- Patients are asked to walk a marked 25-foot course as quickly and safely as possible.
- The examiner records the time and type of assistance (eg, cane, walker, crutches) needed. The rating scale also has categories for patients who are unable to walk.

Although the patient's walking is timed, the time is not used directly but is utilized in conjunction with other factors to rate the patient on an ordinal scale with 10 gradations (Bethoux, 2011). This assessment will be performed for all patients in this study.

8.2.9. Optic Spinal Impairment Score (OSIS)

The OSIS is a scoring system for evaluating the severity of a relapse (Section 10.10). The OSIS VA Subscale Scores will be used to categorize the severity of ON. The OSIS Motor Subscale Scores and Sensory Subscale Scores will be used to categorize the severity of TM.

The OSIS will be assessed at baseline and at the time of On-trial Relapse by the Treating Physician. Further instruction on OSIS evaluation of On-trial Relapse is provided in Section 8.2.3.2.

8.2.10. Ophthalmologic Examination

8.2.10.1. Confrontational Visual Fields

Confrontational VF will be evaluated by the Treating Physician. It is critical for these assessments that the baseline ophthalmologic status be known so that changes in the examination can be used to evaluate prior or ongoing ON. Central scotomas are common in patients

experiencing ON; however, visual field deficits can present with a broad spectrum of patterns (Keltner, 1999).

8.2.10.2. Color Vision

Color vision will be assessed by the Treating Physician or any appropriately trained designee using Ishihara Plates. Loss of color vision can be a marker of ON and is therefore an important assessment tool in NMOSD. Color vision will be assessed in this study using the first 21 Ishihara Plates.

8.2.10.3. Visual Acuity

Visual acuity is usually affected by ON, progressing over a period of hours to days. The Landolt C ring chart will be used to assess VA.

The Landolt C consists of a ring that has a gap, thus looking similar to the letter C. The gap can be at various positions (usually left, right, bottom, top and the 45° positions in between) and the task of the tested person is to decide on which side the gap is. The size of the C and its gap are reduced until the patient makes a specified rate of errors. The minimum perceivable angle of the gap is taken as measure of the visual acuity.

The Treating Physician or an appropriately trained designee will perform the VA test at the protocol specified visits (Section 1.3).

- The test is performed at a distance of 4 meters or 13 feet.
- The Landolt chart is typically recorded as acuity ratio distance (4 meters or 13 feet), so for normal VA it would be recorded as 13/13 or 4/4. Despite being assessed at a distance of 4 meters or 13 feet, sites can also report results using a denominator of 6 (for patients assessed in meters) or 20 (for patients assessed in feet). The appropriate score for each line using these denominators is indicated on the supplied Landolt C ring chart. In this case, a normal VA would be recorded as 20/20 or 6/6. Sites can also choose to enter the score as a decimal, where a normal VA would be 1.0.
- The test should always be done with the best possible correction (ie, wearing glasses) as needed and each eye should be tested independently.

8.2.11. Magnetic Resonance Imaging and Optical Coherence Tomography

Baseline MRI of brain, cervical spine, and thoracic spine (contrast is optional) and OCT examinations should be performed. Exceptions may be granted (eg, based on a recent historical result being available for the study) if approved by the Alexion Medical Monitor.

At the time of relapse, MRI of brain, cervical spine, and/or thoracic spine (contrast is optional) and/or OCT should be performed to evaluate a potential relapse at the discretion of the Investigator when deemed clinically relevant.

Follow-up assessments should be performed promptly after On-trial Relapse if the Investigator decides these are indicated (Section 8.2.3).

8.3. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.3.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the following organs/body systems: skin, head, ears, eyes, nose, throat, neck, lymph nodes, pulse, chest, heart, abdomen, extremities and musculoskeletal.
- A targeted physical examination will include, at a minimum, a body-system relevant examination based upon Investigator judgment and patient symptoms.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- For consistency, all efforts should be made to have the physical examination performed by the same qualified study staff at each study visit.
- Additional Physical Examinations can be performed as medically indicated during the study at the Investigator's discretion.

8.3.2. Height and Weight

Body weight will be measured in pounds or kilograms. Height will be measured in inches or centimeters.

8.3.3. Vital Signs

- Oral, temporal, or axillary temperature (°C or °F), pulse rate, respiratory rate (RR), and systolic and diastolic blood pressure (BP) (mmHg) will be assessed.
- Blood pressure and pulse measurements will be assessed seated with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the patient in a quiet setting without distractions (eg, television, cell phones). Ideally, the same arm for each patient should be used for measurements.

8.3.4. Electrocardiograms

- Single 12-lead ECG will be performed at protocol specified visits in the SoA (see Section 1.3) using an ECG machine to obtain heart rate and measures of PR, QRS, QT, and QTc intervals.
- Patients must be supine for approximately 5-10 minutes before ECG collection and remain supine but awake during ECG collection.
- The Investigator or qualified designee will be responsible for reviewing the ECG to assess whether the ECG is within normal limits and determine the clinical significance of the results. These assessments will be recorded in the source documents and the eCRF.

8.3.5. Patient Safety Card

Before the first dose of study drug, a Patient Safety Card will be provided to study patients to carry with them at all times. The card is provided to increase patient awareness of the risk of infections, especially meningococcal infection and promote quick recognition and disclosure of any potential signs or symptoms of infection experienced by study patients during the course of the study and to inform patients on what actions must be taken if they are experiencing signs or symptoms of infection.

At each visit throughout the study, the study staff will ensure that the patient has the Patient Safety Card.

8.3.6. Prior and Concomitant Medical Review

It is important for Investigators or a qualified designee to review each medication the patient is taking before starting the study and at each visit.

8.3.6.1. Prior Medications

Prior medications and/or vaccines (including vitamins, herbal preparations, and those discussed in the exclusion criteria Section 5.2) and non-drug therapies/procedures (any therapeutic intervention, such as surgery/biopsy or physical therapy) that the patient takes or undergoes within 30 days before the start of Screening or during the Screening Period before the first dose of ravulizumab, any meningococcal vaccine administered within the last 3 years, and any investigational drugs taken within a year of screening, will be recorded in the patient's eCRF. Additionally, all medications or therapies ever used for relapse prevention or acute treatment of NMOSD (including steroids) before the first dose of ravulizumab must be collected.

8.3.6.2. Concomitant Medications

Use of concomitant medications and non-drug therapies/procedures (Section 6.5) will be evaluated during the study. At each visit, patients should be questioned about any new medication or non-drug therapies or changes to concomitant medications and non-drug therapies since the last visit. Concomitant medications and non-drug therapies should be recorded in the source documents and the patient's eCRF.

8.3.7. Clinical Safety Laboratory Assessments

- See Section 10.2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 8 weeks after the last dose of study drug should be

repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the Laboratory Manual and the SoA.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in patient management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.3.8. Suicidal Ideation and Behavior Risk Monitoring

As the study drug is being evaluated for a neurologic indication, patients being treated with the study drug should be monitored appropriately and observed closely for suicidal ideation or behavior or any other unusual changes in behavior, especially at the beginning and end of the course of study drug, or at the time of dose changes.

Baseline assessment of suicidal ideation and behavior as well as intervention-emergent suicidal ideation and behavior will be monitored during this study using the Columbia-suicide severity rating scale (C-SSRS).

There are 2 types of C-SSRS assessments that will be conducted during the study: C-SSRS at Baseline (Section 10.12) and C-SSRS-Since Last Visit (Section 10.13). C-SSRS will be performed by the Treating Physician or an appropriately trained designee at visits specified in the SoA (Section 1.3) to ensure that patients who are experiencing suicidal thoughts or behavior are properly recognized and adequately managed or referred for further evaluation. Additional C-SSRS assessments are permitted as needed.

8.4. Adverse Events and Serious Adverse Events

The definitions of AEs and serious SAEs are specified in Section 10.3.

Adverse events will be reported to the Investigator by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study drug or study procedures, or that caused the patient to discontinue the study drug (see Section 7).

For this trial, information about relapses that do not meet the SAE criteria (Section 10.3) should be recorded in source documents and in the eCRF as part of the Relapse Evaluation Visits and not reported as AEs.

8.4.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All AEs and SAEs will be collected from the signing of the ICF until the last visit at the time points specified in the SoA (Section 1.3).

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 1.3. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of awareness.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to the study drug or study participation, the Investigator must promptly notify the Sponsor.

8.4.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs and AEs of special interest (AESI; as defined in Section 8.4.6), will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (as defined in Section 7.3). Every effort will be made to undertake protocol-specified safety follow-up procedures. Further information on follow-up procedures is provided in Section 10.3.

8.4.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study drug under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- Suspected unexpected serious adverse reactions (SUSAR) must be reported according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will

review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5. Pregnancy

Pregnancy testing must be performed on all WOCBP at protocol-specified timepoints in the SoA (Section 1.3). Pregnancy tests (urine or serum) may also be performed at any time during the study at the Investigator's discretion.

A negative pregnancy test is required for WOCBP before study drug administration.

- Details of all pregnancies in female patients and, if indicated, female partners of male patients will be collected after the start of study drug and until the termination of the pregnancy.
- If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.4
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs. Pregnancy alone is not considered an AE

If a patient becomes pregnant, the study drug must be immediately discontinued, and the Sponsor must be notified as per Section 10.4. Each pregnancy will be followed to term and the Sponsor notified regarding the outcome.

8.4.6. Adverse Events of Special Interest

Meningococcal infections will be collected as adverse events of special interest (AESI).

8.5. Treatment of Overdose

For this study, any dose of study drug greater than that specified in the protocol will be considered an overdose.

Accidental overdose without any association with laboratory abnormalities or clinical symptoms should not be considered as an AE. Overdose must be reported by the Investigator within 24 hours to the Sponsor regardless of its association with or without an AE.

The Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the patient for any AE/SAE.
3. Obtain a plasma sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the timing of the overdose in the CRF.

Decisions regarding dose interruptions will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the patient.

8.6. Pharmacokinetics and Pharmacodynamics

- Blood samples for determination of serum drug concentrations and PD assessments will be collected before and after administration of study drug at the time points as specified in the SoA (Section 1.3).
- Cerebrospinal fluid (CSF) samples for PK and PD assessments are optional at protocol specified timepoints (Section 1.3) and will only be obtained from patients who consent to CSF collection.
- Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded on the eCRF and the central laboratory requisition form.
- Additional information on sample collection, including blood volume requirements, is provided in the Laboratory Manual.

8.6.1. Sample Collection During the Study Period

- Baseline (B) and trough (T) PK and PD blood samples will be collected at predose, within 90 minutes before administering study drug at visits specified in the SoA (Section 1.3). The predose blood sample may be drawn through the venous access created for the dose infusion, prior to administration of the dose.
- Postdose (P) PK and PD blood samples will be collected postdose, within 60 minutes after completing study drug infusion. The postdose blood samples will be drawn from the patient's opposite, non-infused arm.
- Blood samples at a non-dosing visit can be collected at any time.
- In the event of an unscheduled visit, PK and PD blood sample will be collected as soon as possible.

8.6.2. Sample Collection During On-trial Relapse

Blood sample for PK and PD analyses will be collected at any time during the scheduled Relapse Evaluation Visit.

However, if the relapse-associated blood sample collection schedule coincides with a regular sample collection specified in the SoA (Section 1.3), the directions for regular PK and PD sample collection during the study (Section 8.6.1) should be followed.

During On-trial Relapse, if the patient receives PE/PP and a supplemental dose of ravulizumab at the Relapse Evaluation Visit, 3 blood samples for PK and PD should be collected at the following intervals:

1. Approximately 5 to 90 minutes prior to PE/PP/IVIg
2. After PE/PP/IVIg and before study drug infusion
3. Within 60 minutes after the completion of study drug infusion

If a patient receives PE/PP/IVIg at any visit other than the Relapse-Evaluation Visit, blood samples for PK and PD will be collected immediately before and after each session of PE/PP/IVIg. A postdose sample, (ie, within 1 hour after completion of supplemental study drug infusion), will also be collected.

8.7. Genetics

There are no prespecified genetic analyses in this study.

8.8. Biomarker Research

8.8.1. Exploratory Biomarker Research

Blood samples for biomarker research will be collected from all patients at timepoints specified in the SoA (Section 1.3):

CSF samples are optional samples for biomarker research and should only be collected from patients who have consented to CSF sample collection.

- Biomarkers will be measured and include, but are not limited to, assessments of the following:
  - AQP4-Ab at protocol-specified time points (Section 1.3 SoA), including during the Relapse Evaluation Period (see Section 8.2.3.2 for details).
  - Complement products
  - Markers of neuroinflammation, such as interleukin 6 (IL-6)
  - Markers of neural injury, such as neurofilament light chain (NfL)

Deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) sample collection is optional. DNA and RNA blood samples must only be collected from patients that consent to it. DNA and RNA testing on these samples include assessments of the following including, but not limited to, specific candidate genes/genome-wide analysis:

- Research related to ravulizumab, NMOSD, and related diseases
- Developing tests/assays, including diagnostic tests related to ravulizumab and NMOSD

8.8.2. Future Biomarker Research

For patients that consent to DNA and RNA testing, future DNA and RNA testing on these samples include assessments of the following:

- Research related to ravulizumab, NMOSD, and related diseases
- Developing tests/assays, including diagnostic tests related to ravulizumab and NMOSD

Remaining samples from pharmacokinetic, pharmacodynamic, immunogenicity, and biomarker testing will be stored for future biomarker research. Analyses may be performed on biomarker variants thought to play a role in NMOSD activity/progression or treatment response to

ravulizumab. These samples may also be used to develop methods, assays, prognostics and/or companion diagnostics related to the study drug target, disease process, pathways associated with disease state, and/or mechanism of action of the study drug.

Samples may be stored for a maximum duration according to local regulations following the last patient's last visit for the study at a facility selected by the Sponsor to enable further analyses.

8.9. Immunogenicity Assessments

Anti-drug antibodies (ADAs) to ravulizumab will be evaluated in serum samples collected predose (within 5-90 minutes prior to the start of infusion of study drug) from all patients according to the SoA (Section 1.3).

Additionally, serum samples should also be collected at the final visit from patients who discontinued study drug or were withdrawn from the study.

Serum samples will be screened for antibodies binding to ravulizumab and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to ravulizumab and/or further characterize the immunogenicity of ravulizumab.

The detection and characterization of antibodies to ravulizumab will be performed using a validated assay method by or under the supervision of the Sponsor. Samples may be further characterized to determine the titer and the presence of neutralizing antibodies if deemed necessary. Samples may be stored for a maximum duration according to local regulations following the last patient's last visit for the study at a facility selected by the Sponsor to enable further analysis of immune responses to ravulizumab.

8.10. Medical Resource Utilization and Health Economics

Medical resource utilization and health economics data, associated with medical encounters, will be collected in the CRF by the Investigator and study-site personnel for all patients throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses and will include:

- Number of surgeries, and other selected procedures (inpatient and outpatient)
- Duration of hospitalization
- Number and type of diagnostic and therapeutic tests and procedures

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The time to first adjudicated On-trial Relapse will be evaluated using the log-rank test; the null hypothesis will be that there is no difference in the survival curves of the ravulizumab and the placebo treatment groups. The alternative hypothesis will be that there is a difference between the two survival curves, and ravulizumab is superior to placebo.

The adjudicated On-trial ARR will be presented with a 95% confidence interval (CI) to provide an estimate of the adjudicated On-trial ARR for patients treated with ravulizumab. The null hypothesis will be that the mean adjudicated On-trial ARR is equal to 0.25 relapse/patient-year. The alternative hypothesis will be that the mean adjudicated On-trial ARR is not equal to 0.25.

For HAI the null hypothesis will be that the odds of a better outcome are the same between the ravulizumab arm and the placebo arm. The alternative hypothesis will be that there is a difference in the odds of a better outcome between the treatment arms and that ravulizumab has a higher odds of a better outcome.

For the EQ-5D index and the EQ-5D VAS, the null hypothesis will be that there is no difference between the distribution of the ravulizumab arm and the placebo arm. The alternative hypothesis will be that there is a difference between the distribution of the treatment arms and that ravulizumab is superior to placebo.

For the EDSS the null hypothesis will be that the odds of a worse outcome are the same between the ravulizumab arm and the placebo arm. The alternative hypothesis will be that there is a difference in the odds of a worse outcome between the treatment arms and that the odds of a worse outcome are higher in the placebo arm.

9.2. Sample Size Determination

This is an open-label, external placebo-controlled study to evaluate ravulizumab in NMOSD patients with the primary endpoint of time to first adjudicated On-trial Relapse. The placebo treatment arm in Study ECU-NMO-301 will serve as the external control.

The sample size and power calculation assumptions for this study using the primary endpoint, time to first adjudicated On-trial Relapse, are as follows:

- Log-rank test for comparison of ravulizumab to placebo
- 47 patients in the placebo treatment group
- Power 90%
- Two-sided 5% level of significance
- Drop-out rate 2-10%
- Relapse-free rate of 92% for the ravulizumab arm at 12 months
- Relapse-free rate of 63% for the placebo arm at 12 months

With these assumptions, a maximum sample size of approximately 55 patients in the ravulizumab treatment group provides at least 90% power to detect a treatment difference in time to first positively adjudicated On-trial Relapse.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Table 10: Populations for Analyses

Population	Description
Full Analysis Set (FAS)	All patients who receive at least 1 dose of study drug.
Safety Set	All patients who receive at least 1 dose of study drug.
Per Protocol Set (PPS)	The PPS is a subset of the FAS, excluding patients with important protocol deviations. The PP population will include all patients who: • Have no important protocol deviations or key inclusion/exclusion criteria deviations that might potentially affect efficacy, • Patients who took at least 80% of the required treatment doses while they were in the treatment period. Further details will be provided in the statistical analysis plan (SAP).
Pharmacokinetic and Pharmacodynamic Analysis Set (PKPDAS)	All patients who receive at least 1 dose of study drug and who have at least one evaluable PK or PD result.

9.4. Statistical Analyses

The primary analysis will be conducted when all patients have completed the Primary Treatment Period. This analysis will include all efficacy, safety, PK/PD, and immunogenicity study data for regulatory submission purposes and will be the final analysis of the Primary Treatment Period. The original SAP to support the primary analysis was developed and finalized shortly after the original protocol was final. If necessary, a final SAP will be developed prior to the completion of the long-term extension period to describe any additional long-term efficacy and safety analyses. This section is a summary of the planned statistical analyses of the primary and secondary efficacy endpoints and the safety analyses.

Summary statistics will be computed and displayed by treatment group and by visit, where applicable. Descriptive statistics for continuous variables will minimally include the number of patients, mean, standard deviation, minimum, median, and maximum. For categorical variables, frequencies, and percentages will be presented. Graphical displays will be provided as appropriate. All statistical analyses will be performed based on a 2-sided Type I error of 5% unless noted otherwise. Missing data will not be imputed unless otherwise indicated in the described analysis in the SAP.

Analyses will be performed using the SAS® software Version 9.4 or higher.

9.4.1. Efficacy Analyses

To account for potential differences in baseline characteristics between the ravulizumab group and the external placebo control, sensitivity analyses of efficacy endpoints will include covariate adjustment methodologies, as warranted. Details are provided in the SAP.

9.4.1.1. Primary Endpoint

The primary efficacy endpoint is time to first adjudicated On-trial Relapse. The trial will be considered to have met its primary efficacy objective if a statistically significant difference (ie, p-value ≤ 0.05) is observed between the ravulizumab treatment group and the placebo group for the primary endpoint of the time to first adjudicated On-trial Relapse. The comparison of the treatment groups for the primary endpoint will use a log-rank test. Hazard ratio and risk reduction will be summarized from a Cox proportional hazards model. If there is no observed event in a treatment arm, then Firth's Penalized Likelihood (Heinze, 2001) will be used to estimate the hazard ratio, risk reduction, and the profile likelihood 95% CIs. Confidence intervals (95%) will be presented for the estimated proportion of patients that are relapse-free at various timepoints (eg, Week 24, Week 48) based on the complementary log-log transformation. Kaplan-Meier curves for both treatment groups will be produced.

Those patients who, for COVID-19-related reasons as determined by the Investigator and documented in the eCRF (eg, infected with or exposure to COVID-19, quarantine, travel restrictions), received a dose of ravulizumab > 35 days late or missed a dose altogether will be censored at the time of the missed dose, if the missed or delayed dose occurred before the EOPT Visit or the first adjudicated On-trial Relapse. To balance the evaluation period, patients in the placebo treatment group who were followed longer than patients in the ravulizumab treatment group will be censored at the maximum time observed in the ravulizumab treatment group. Any relapses that had been observed among patients in the placebo group after that time will not be included in the primary analysis.

Sensitivity analyses of the primary endpoint will be described in the SAP.

9.4.1.2. Secondary Endpoint(s)

For those patients who, for COVID-19 related reasons as determined by the Investigator and documented in the eCRF (eg, infected with or exposure to COVID-19, quarantine, travel restrictions), received a dose of ravulizumab > 35 days late or missed a dose altogether, for endpoints involving the change from baseline, the change from baseline to the last value before the missed dose, if the missed or delayed dose occurred before the EOPT Visit or the 6-week Post-relapse Visit, will be summarized and analyzed.

9.4.1.2.1. Adjudicated On-trial ARR

The adjudicated On-trial ARR will be presented showing the ravulizumab treatment group estimate and 95% CI from a Poisson regression model in which the log of time in the study period will be used as the offset variable and historical ARR will be a covariate in the model. This endpoint will be considered statistically significant if the 2-sided p-value is ≤ 0.05, and if the adjudicated On-trial ARR < 0.25 or if 0 relapses are observed.

For those patients who, for COVID-19 related reasons as determined by the Investigator and documented in the eCRF (eg, infected with or exposure to COVID-19, quarantine, travel restrictions), received a dose of ravulizumab > 35 days late or missed a dose altogether, any relapse that occurred during the time interval from the missed dose until the start of the next dose will be excluded from the ARR calculations and summaries.

9.4.1.2.2. EuroQoL 5 Dimension (EQ-5D) Index Score and EQ-5D VAS

The change from baseline in the EQ-5D index score to the 6-week post-relapse/End of Primary Treatment Period time point (ie, for the placebo arm: 6 weeks post-relapse for the patients who have relapses, or Study ECU-NMO-301 end of study (EOS) for patients who did not have relapses; for the ravulizumab arm: the 6 week post-relapse visit for the first observed relapse for the patients who have relapses and the EQ-5D index score from the End of Primary Treatment Period visit for patients who did not have a relapse) will be analyzed using an analysis of covariance (ANCOVA), in which the ranks of the change from baseline will be the dependent variable, with treatment as a factor and the ranks of the baseline values as a covariate. Baseline is defined as the last available assessment prior to treatment for all patients regardless of their treatment group.

The changes from baseline to the 6-week post-relapse/EOPT Period time point in EQ-5D VAS will be analyzed as described for the change in EQ-5D index score.

9.4.1.2.3. Expanded Disability Status Scale (EDSS)

The change from baseline in the EDSS score to the 6-week post-relapse/EOPT Period analysis time point will be calculated as described for the EQ-5D endpoints. For the EDSS, this change from baseline will be categorized into clinically important worsening (no worsening, clinical worsening). This endpoint will be analyzed using a logistic regression model including treatment group and baseline EDSS as a covariate. Details will be provided in the SAP.

9.4.1.2.4. Hauser Ambulation Index (HAI)

The change from baseline in the HAI score to the 6-week post-relapse/EOPT Period analysis time point will be calculated as described for the EQ-5D endpoints. For the HAI, this change from baseline will be categorized into clinically important changes (clinical improvement, stable, clinical worsening). This 3-level endpoint will be analyzed using a proportional odds model including treatment group and baseline HAI as a covariate. Details will be provided in the SAP.

9.4.1.2.5. Accounting for Multiple Comparisons

A closed testing procedure will be applied to control the type I error for the analyses of the primary and secondary endpoints. If the primary endpoint is statistically significant in favor of ravulizumab, the secondary endpoints will be evaluated according to the following rank order:

1. Adjudicated On-trial ARR
2. Clinically important changes from baseline in ambulatory function as measured by HAI
3. Change from baseline in EQ-5D index score
4. Change from baseline in EQ-5D VAS score

5. Clinically important worsening from baseline in EDSS score

The hypothesis testing will proceed from highest rank (#1) the adjudicated On-trial ARR to the lowest rank (#5) EDSS score, and if statistical significance is not achieved at an endpoint ($p > 0.05$), then endpoints of lower rank will not be considered to be statistically significant. Confidence intervals and p-values will be presented for all secondary efficacy endpoints for descriptive purposes, regardless of the outcome of the closed testing procedure.

Additional information on multiple comparisons is detailed in the SAP.

9.4.1.3. Tertiary/exploratory endpoint(s)

Summaries and analyses of tertiary and exploratory endpoints will be described in the SAP.

9.4.2. Safety Analyses

All safety data will be summarized using the Safety Set.

9.4.2.1. Analysis of Adverse Events

The analysis and reporting of AEs will be based on treatment-emergent adverse events (TEAEs), defined as AEs with onset on or after the first dose of ravulizumab. The incidence of TEAEs will be summarized by system organ class (SOC) and preferred term, with additional summaries showing severity, relationship to study drug, TEAEs leading to study drug discontinuation, and TEAEs resulting in death. Summaries of treatment-emergent serious adverse events (TESAEs) will also be summarized by SOC and preferred term, with an additional summary showing relationship to study drug. These summaries will be presented by treatment group (ravulizumab, placebo).

9.4.2.2. Analysis of Clinical Laboratory Parameters, Vital Sign Measurements and Electrocardiogram Parameters

Laboratory measurements as well as their changes from Baseline at each visit and shift from baseline, if applicable, will be summarized. ECGs, including ECG interpretation heart rate, PR, QRS, QT, and QTc intervals, and vital signs will also be summarized.

9.4.2.3. Other Safety Analyses

The number and percentage of patients in each of the C-SSRS categories as well as shifts from baseline will be presented.

9.4.3. Demographics and Baseline Characteristics

Patient demographic and baseline characteristics will be summarized by treatment group, using the Safety Set. Summary statistics will be presented. No formal hypothesis testing will be performed.

9.4.4. Patient Disposition

The number of patients screened, treated, completing the study, discontinued the study, reasons for discontinuation, and those included in each analysis set will be summarized.

Important protocol deviations will be summarized by prespecified deviation categories.

9.4.5. Medical/Surgical History and Neuromyelitis Optica Spectrum Disorder History

The medical and surgical history will be summarized by the Medical Dictionary for Regulatory (MedDRA) Activities, Version 21.0, or later by SOC and PT. NMOSD History will also be summarized.

9.4.6. Prior and Concomitant Medications

Any medication taken prior to the first dose of study drug will be considered as prior medications; and any medication taken on or after the first dose of study drug will be considered as concomitant medications. Prior and concomitant medications will be summarized for all patients in the Safety Analysis Set, including ISTs for relapse prevention and acute relapse treatment. Medications will be coded using the World Health Organization Drug Dictionary (WHO Drug; the most current version available at the time of the analyses).

9.4.7. Pharmacokinetic, Pharmacodynamic, and Anti-Drug Antibody Analyses

Individual serum concentration data for all patients who receive at least 1 dose of ravulizumab and who have evaluable PK data will be used to derive PK parameters for ravulizumab.

Graphs of mean serum concentration-time profiles will be constructed. Graphs of serum concentration-time profiles for individual patients may also be provided. Actual dose administration and sampling times will be used for all calculations. Descriptive statistics will be calculated for serum concentration data at each sampling time, as appropriate. Assessment of population-PK may be considered using data from this study or in combination with data from other studies.

Pharmacodynamic analyses will be performed for all patients who receive at least 1 dose of ravulizumab and who have evaluable PD data.

Descriptive statistics will be presented for all ravulizumab PD endpoints at each sampling time (Section 1.3). The PD effects of ravulizumab will be evaluated by assessing the absolute values and changes and percentage changes from baseline in free C5 serum concentrations over time, as appropriate. Assessments of ravulizumab PK/PD relationships may be explored using data from this study or in combination with data from other studies.

For assessment of immunogenicity, the presence of confirmed positive ADAs will be summarized. Additionally, following confirmation of positive ADAs, samples will be assessed for ADA titer and presence of neutralizing antibodies.

9.4.8. Medical Resource Utilization and Health Economics

Descriptive statistics will be provided for the following:

- The number of days of hospitalizations for the 2 years prior to Screening (for all hospitalizations, and those related to NMOSD Relapse) and the ratio of the number of days of hospitalization in the 2-year period.
- The number of days of hospitalizations during the study period (for all hospitalizations, and for adjudicated On-trial Relapses) and the ratio of the number of days of hospitalizations and days in the Study Period.

The following endpoints will be summarized by treatment group showing total counts, event rates as per patient-years of follow-up in the study period, and the number and percentage of patients:

- With surgeries, and other selected procedures (inpatient or outpatient)
- With any diagnostic or therapeutic test or procedures
- For each type of diagnostic and therapeutic test and procedure, as coded by MedDRA (version 21.0 or higher) by SOC and Preferred Term.

9.5. Interim Analysis

The primary analysis will be conducted when all patients have completed the Primary Treatment Period. This analysis will include all efficacy, safety, PK/PD, and immunogenicity study data for regulatory submission purposes and will be the final analysis of the Primary Treatment Period. This analysis will not be considered an interim analysis. Interim analyses that include data collected during the Long-term Extension may be performed to support submission requirements.

9.6. Data Monitoring Committee (DMC)

This study will not include a DMC.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the patient and answer all questions regarding the study.
- Patients must be informed that their participation is voluntary. Patients will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the patient was screened in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF(s).
- Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the patient.

Patients who are rescreened are required to sign a new ICF (see Section 5.4).

10.1.4. Data Protection

- Patients will be assigned a unique identifier by the Sponsor. Any patient records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.
- The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient who will be required to give consent for their data to be used as described in the informed consent
- The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Dissemination of Clinical Study Data

Study-related information and study results may be posted on publicly accessible clinical study databases (eg, the US website www.clinicaltrials.gov or the EU website: Http://www.clinicaltrialsregister.eu), as appropriate, and in accordance with national, regional, and local regulations.

10.1.6. Data Quality Assurance

- All patient data relating to the study will be recorded on a printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The

Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 2 years after the last marketing application approval, or if not approved, 2 years following the discontinuance of the test article for investigation, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. The Investigator or designee will prepare and maintain adequate and accurate source documents (eg, medical records, ECGs, AE and concomitant medication reporting, raw data collection forms) designed to record all observations and other pertinent data for each patient.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available. Source documents are filed at the Investigator's site.

10.1.8. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of patients and will be marked by the date that the first site is opened.

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of patients by the Investigator
- Discontinuation of further study drug development
- Withdrawal of the favorable opinion or the approval
- Inability to adjust the required maximum sum of insurance

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the patient and should assure appropriate patient therapy and/or follow-up.

10.1.9. Publication Policy

The full terms regarding publication of the results of this study are outlined in the applicable Clinical Study Agreement.

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 11 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study drug administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study drug decision or response evaluation, the results must be entered into the CRF.

- Protocol-specific requirements for inclusion or exclusion of patients are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Women of childbearing potential should only be enrolled after a negative serum pregnancy test. Additional pregnancy testing (urine or serum) should be performed per the time points specified in the SoA (Section 1.3).
- Investigators must document their review of each laboratory safety report.

Table 11: Clinical Laboratory Tests

Chemistry Panel Sodium Potassium Chloride Bicarbonate Blood urea nitrogen Creatinine Glucose Alkaline phosphatase Alanine amino transferase (ALT) Aspartate amino transferase (AST) Total bilirubin Albumin Total protein Uric acid Calcium Magnesium HIV (1 and 2) testing **Complete Blood Count (CBC) & Differential** White blood cell count (WBC) White blood cell differential Red blood cell count (RBC) RBC mean corpuscular volume (MCV) RBC distribution width Hemoglobin Hematocrit Platelet count **Urinalysis** Appearance Specific gravity pH Protein Blood Glucose Ketone Bilirubin Urobilinogen Nitrite	**Others** Human Chorionic Gonadotropin (β-HCG) Anti-Aquaporin 4 Antibody (AQP4-IgG Ab) Serum Pharmacokinetics (PK) and Serum Free Complement Factor 5 (Free C5) Anti-drug Antibody (ADA) FSH[1]

[1] To confirm postmenopausal status in selected female patients.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Adverse Event Definition

Adverse Event Definition
• An AE is any untoward medical occurrence in a patient or clinical study patient, temporally associated with the use of study drug, whether or not considered related to the study drug. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study drug.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study drug administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Serious Adverse Event Definition

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as an AE that, at any dose:

1. Results in death

2. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

3. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

4. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

5. Is a congenital anomaly/birth defect

6. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording and Follow-Up of Adverse Event and/or Serious Adverse Event

Adverse Event and Serious Adverse Event Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE or SAE information in the CRF.
- It is not acceptable for the Investigator to send photocopies of the patient's medical records to Alexion in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Alexion. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to Alexion.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories from National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0, published 27 Nov 2017:

- Grade 1: Mild (awareness of sign or symptom, but easily tolerated)
- Grade 2: Moderate (discomfort sufficient to cause interference with normal activities)
- Grade 3: Severe (incapacitating, with inability to perform normal activities)

- Grade 4: Life-threatening
- Grade 5: Fatal

Changes in the severity of an AE should be documented to allow an assessment of the AE duration at each level of intensity to be evaluated. Adverse events characterized as intermittent require documentation of onset and duration of each episode, if the severity of the intermittent event changes.
An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between the study drug and each occurrence of each AE or SAE. An Investigator causality assessment must be provided for all AEs (both nonserious and serious). This assessment must be recorded in the eCRF and on any additional forms, as appropriate. **The definitions for the causality assessments are as follows:**
  - **Not related (unrelated): There is no causal association with study drug**
  - **Related: There is causal (temporal) association to the study drug. Other conditions (concurrent illness, concurrent medication reaction, or progression/expression of disease state) do not appear to explain the event; the event corresponds with the known pharmaceutical profile; improvement on discontinuation; reappearance on rechallenge.**
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration will be considered and investigated.
- This protocol will use the current Investigator's Brochure as the Reference Safety Document. The expectedness and reporting criteria of an SAE will be determined by the Sponsor, based on the Reference Safety Document. The Investigator will also consult the Investigator's Brochure (IB) in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
  - There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to Alexion. However, **it is very important that the Investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor or designee.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Events and Serious Adverse Events

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Alexion to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a patient dies during participation in the study or during a recognized follow-up period, the Investigator will provide Alexion with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to Alexion within 24 hours of receipt of the information.

10.3.4. Reporting of Serious Adverse Events

Serious Adverse Event Reporting to Alexion or designee via an Electronic Data Collection Tool

- All SAEs will be recorded and reported to Alexion or designee immediately and within 24 hours of awareness.
- The primary mechanism for reporting an SAE to Alexion or designee will be the electronic data capture (EDC) tool.
- If the electronic system is unavailable at the time that the Investigator or site becomes aware of an SAE, the site will use the paper Contingency Form for SAE reporting via fax or email. Facsimile transmission or email may be used in the event of electronic submission failure.
  - Email: [redacted] or Fax: [redacted]
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- When further information becomes available, the EDC should be updated within 24 hours with the new information and an updated SAE report should be submitted to Alexion Global Drug Safety (GDS).
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study patient or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form to Alexion GDS.

Serious Adverse Event Reporting to Alexion via Paper Report Form

- All SAEs will be recorded and reported to Alexion or designee immediately and within 24 hours of awareness.
- SAEs will be reported using the Safety Reporting Form and submitted to Alexion GDS. The Investigator must complete, sign, and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy via email or facsimile to the contact information provided below:
  - Email: [redacted] or Fax: [redacted]
  -
- Additional follow-up information, if required or available, should be entered into the eCRF and sent to Sponsor within 24 hours of the Investigator or study site staff becoming aware of this additional information via the reporting process outlined above.
- For all SAEs, the Investigator must provide the following:
  - Appropriate and requested follow-up information in the time frame detailed above
  - Causality of the serious event(s)
  - Treatment of/intervention for the SAE(s)
  - Outcome of the serious event(s)
  - Medical records and laboratory/diagnostic information
- All paper forms and follow-up information submitted to Alexion GDS must be accompanied by a cover page signed by the Investigator.
- Paper source documents and/or reports should be kept in the appropriate section of the study file.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Definitions

10.4.1.1. Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study drug, additional evaluation should be considered.

10.4.1.2. Women in the Following Categories Are Not Considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy
- For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

    Note: Documentation can come from the site personnel's: review of the patient's medical records, medical examination, or medical history interview.

3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        – A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2. Contraception Guidance:

Before receiving study drug, female patients who consider themselves to be postmenopausal must provide evidence of postmenopause based on amenorrhea for at least 1 year prior to Day 1 visit. Confirmatory serum follicle-stimulating hormone level (> 30 IU/L) may be obtained by the Investigator at screening. In the absence of 1 year of amenorrhea, multiple elevated FSH levels

will be required. The reason for not obtaining an FSH should be documented by the Investigator at the time of screening.

Patients of childbearing potential must use a highly effective or acceptable method of contraception (as defined below) starting at Screening and continuing for at least 8 months after the last dose of study drug.

Highly effective contraceptive methods include:

1. Hormonal contraception associated with inhibition of ovulation
2. Intrauterine device
3. Intrauterine hormone-releasing system
4. Bilateral tubal occlusion
5. Vasectomized partner provided that the partner is the patient's sole sexual partner
6. Sexual abstinence defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug treatment; reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient

Acceptable contraceptive methods include:

A combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods)

The above-listed method(s) of contraception chosen for an individual patient can be determined by the Investigator with consideration for the patient's medical history and concomitant medications.

Patients with a spouse/partner of childbearing potential or a pregnant or breastfeeding spouse or partner must agree to use double barrier contraception (male condom plus appropriate barrier method for the female partner) while on treatment and for at least 8 months after the last dose of study drug. Double barrier contraception is required even with documented medical assessment of surgical success of a vasectomy.

Male patients must not donate sperm and female patients must not donate ova while on treatment and for at least 8 months after the last dose of study drug.

10.4.3. Pregnancy Testing

Patients of childbearing potential should only be included after a menstrual period and a negative highly sensitive serum pregnancy test.

Additional pregnancy testing should be performed per the time points specified in the SoA (Section 1.3).

Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

10.4.4. Collection of Pregnancy Information

10.4.4.1. Male Patients with Partners Who Become Pregnant

- The Investigator will attempt to collect pregnancy information on any male patient's female partner who becomes pregnant while the male patient is in this study. This applies only to male patients who receive study drug.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

10.4.4.2. Female Patients Who Become Pregnant

- The Investigator will collect pregnancy information on any female patient who becomes pregnant while participating in this study. The initial Information will be recorded on the Pregnancy Outcome and Breastfeeding Form and submitted to the Sponsor within 24 hours of learning of a patient's pregnancy.
- The patient will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the patient and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 3 months beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study drug by the Investigator will be reported to the Sponsor as described in Section 8.4. While the Investigator is not obligated to actively seek this information in former study patients, he or she may learn of an SAE through spontaneous reporting.
- Any female patient who becomes pregnant while participating in the study will discontinue study drug, and each pregnancy will be followed to term and the Sponsor notified regarding the outcome.

10.5. Appendix 5: Diagnostic Criteria for Neuromyelitis Optica Spectrum Disorder

International Panel for NMO Diagnosis Diagnostic Criteria for NMOSD with AQP4-IgG (Wingerchuk, 2015**)**: All 3 criteria must be met for a diagnosis of NMOSD in this study.

1. At least 1 core clinical characteristic:
    a. Optic neuritis
    b. Acute myelitis
    c. Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting
    d. Acute brainstem syndrome
    e. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD typical diencephalic MRI lesions
    f. Symptomatic cerebral syndrome with NMOSD-typical brain lesions visualized on MRI
2. Positive test for anti-AQP4 Ab using best available detection method (cell-based assay required in this study)
3. Exclusion of alternative diagnosis

10.6. Appendix 6: Expanded Disability Status Scale (EDSS)

The Neurostatus EDSS (using the Kurtzke neurologic evaluation) is a method of quantifying disability in Multiple Sclerosis (MS). The EDSS replaced the previous Disability Status Scales used in MS.

The EDSS quantifies disability in 7 Functional Systems (FS) and allows neurologists to assign a Functional System Score (FSS) in each of these. The FS are:

- pyramidal
- cerebellar
- brainstem
- sensory
- bowel and bladder
- visual
- cerebral

EDSS steps 1.0 to 4.0 refer to people with MS who are fully ambulatory. EDSS steps 4.5 to 9.5 are predominantly defined by the impairment to ambulation.

Neurostatus Expanded Disability Status Scale	
0	Normal neurological examination (all FS grade 0)
1.0	No disability, minimal signs in one FS (one FS grade 1)
1.5	No disability, minimal signs in more than one FS (more than one FS grade 1)
2.0	Minimal disability in one FS (one FS grade 2, others 0 or 1)
2.5	Minimal disability in two FS (two FS grade 2, others 0 or 1)
3.0	Moderate disability in one FS (one FS grade 3, others 0 or 1) though fully ambulatory; or mild disability in three or four FS (three/four FS grade 2, others 0 or 1) though fully ambulatory
3.5	Fully ambulatory but with moderate disability in one FS (one FS grade 3) and mild disability in one or two FS (one/two FS grade 2) and others 0 or 1; or fully ambulatory with two FS grade 3 (others 0 or 1); or fully ambulatory with five FS grade 2 (others 0 or 1)

4.0	Ambulatory without aid or rest for ≥ 500 meters; up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps
4.5	Ambulatory without aid or rest for ≥ 300 meters; up and about much of the day, characterized by relatively severe disability usually consisting of one FS grade 4 and combination of lesser grades exceeding limits of previous steps
5.0	Ambulatory without aid or rest for ≥ 200 meters (usual FS equivalents include at least one FS grade 5, or combinations of lesser grades usually exceeding specifications for step 4.5)
5.5	Ambulatory without aid or rest for ≥ 100 meters
6.0	Unilateral assistance (cane or crutch) required to walk at least 100 meters with or without resting
6.5	Constant bilateral assistance (canes or crutches) required to walk at least 20 meters without resting
7.0	Unable to walk 5 meters even with aid, essentially restricted to wheelchair; wheels self and transfers alone; up and about in wheelchair some 12 hours a day
7.5	Unable to take more than a few steps; restricted to wheelchair; may need some help in transferring and in wheeling self
8.0	Essentially restricted to bed or chair or perambulated in wheelchair, but out of bed most of day; retains many self-care functions; generally has effective use of arms
8.5	Essentially restricted to bed much of the day; has some effective use of arm(s); retains some self-care functions
9.0	Helpless bed patient; can communicate and eat
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow
10.0	Death due to MS

10.7. Appendix 7: EuroQoL 5 Dimensions (EQ-5D-3L)

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (e.g. work, study, housework, family or leisure activities)

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

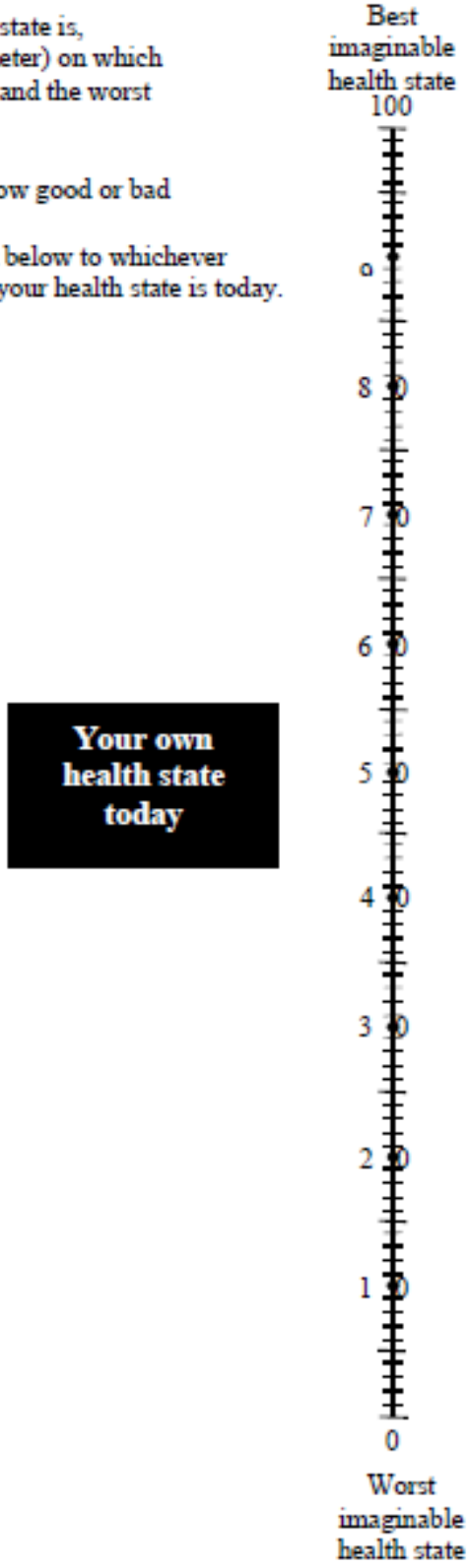
I am not anxious or depressed ❑

I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion.
Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.



To be completed by Study Site			
Study Number: ALXN1210-NMO-307	Subject ID: _____	Interviewer: _____	Date Completed: _____

Health Questionnaire

English version for the USA

SCRIPT FOR FACE-TO-FACE ADMINISTRATION

GENERAL INTRODUCTION

It is suggested that the interviewer follows the script of the EQ-5D. Although allowance should be made for the interviewer's particular style of speaking, the wording of the questionnaire instructions should be followed as closely as possible. In the case of EQ-5D descriptive system on page 2 of the questionnaire, the precise wording must be followed.

It is recommended that the interviewer has a copy of the EQ-5D in front of him or her and gives a second copy of the EQ-5D to the respondent for reference. This enables the respondent's answers to be entered directly on the EQ-5D by the interviewer on behalf of the respondent (i.e. the appropriate boxes on page 2 are marked and the scale on page 3 is marked at the point indicating the respondent's 'own health state today').

If the respondent asks for clarification, the interviewer can help by re-reading the question verbatim. The interviewer should not try to offer his or her own explanation but suggest that the respondent uses his or her own interpretation.

If the respondent has difficulty with regard to which response to choose, the interviewer should repeat the question verbatim and ask the respondent to answer in a way that most closely resembles his or her thoughts about his or her health state today.

INTRODUCTION TO EQ-5D

We are trying to find out what you think about your health. I will first ask you a few brief and simple questions about your own health state today. I will then ask you to do a rather different task that involves rating your health on a measuring scale. I will explain the tasks fully as I go along, but please interrupt me if you do not understand something or if things are not clear to you. Please also remember that there are no right or wrong answers. We are interested here only in your personal view.

EQ-5D DESCRIPTIVE SYSTEM - PAGE 2: INTRODUCTION

First I am going to read out some questions. Each question has a choice of three answers. Please tell me which answer best describes your own health state TODAY.

Do not choose more than one answer in each group of questions.

(Note for interviewer: it may be necessary to remind the respondent regularly that the timeframe is today)

EQ-5D DESCRIPTIVE SYSTEM - PAGE 2: TASK

MOBILITY

First I'd like to ask you about mobility.

Question 1:

1. **Would you say you have… no problems in walking about?**
2. **Would you say you have… some problems in walking about?**
3. **Are you confined to bed?**

(Note for administrator: mark the appropriate box on the EQ-5D questionnaire)

SELF-CARE

Next I'd like to ask you about self-care.

Question 2:

1. **Would you say you have… no problems with self-care?**
2. **Would you say you have… some problems washing or dressing yourself?**
3. **Are you unable to wash or dress yourself?**

(Note for administrator: mark the appropriate box on the EQ-5D questionnaire)

USUAL ACTIVITIES

Next I'd like to ask you about your usual activities, for example work, study, housework, family or leisure activities.

Question 3:

1. **Would you say you have… no problems with performing your usual activities?**
2. **Would you say you have… some problems with performing your usual activities?**
3. **Are you unable to perform your usual activities?**

(Note for administrator: mark the appropriate box on the EQ-5D questionnaire)

PAIN / DISCOMFORT

Next I'd like to ask you about pain or discomfort.

Question 4: Would you say you have…

1. **No pain or discomfort?**
2. **Moderate pain or discomfort?**
3. **Extreme pain or discomfort?**

(Note for administrator: mark the appropriate box on the EQ-5D questionnaire)

ANXIETY / DEPRESSION

Finally I'd like to ask you about anxiety or depression.

Question 5: Would you say you are…

1. **Not anxious or depressed?**
2. **Moderately anxious or depressed?**
3. **Extremely anxious or depressed?**

(Note for administrator: mark the appropriate box on the EQ-5D questionnaire)

EQ VAS - PAGE 3: INTRODUCTION

I would now like to ask you to do a rather different task.

To help you say how good or bad your health state is, I'd like you to look at the scale, which is similar to a thermometer. The best health state you can imagine is marked 100 (one hundred) at the top of the scale and the worst state you can imagine is marked 0 (zero) at the bottom.

EQ VAS - PAGE 3: TASK

I would now like you to tell me the point on this scale where you would put your own health state today.

Thank you for taking the time to answer these questions.

10.8. Appendix 8: Short Form Health Survey (SF-36)

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐1	☐2	☐3	☐4	☐5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐1	☐2	☐3	☐4	☐5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c. Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d. Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e. Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f. Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g. Walking more than a mile	☐ 1	☐ 2	☐ 3
h. Walking several hundred yards	☐ 1	☐ 2	☐ 3
i. Walking one hundred yards	☐ 1	☐ 2	☐ 3
j. Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b. Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c. Were limited in the kind of work or other activities	☐1	☐2	☐3	☐4	☐5
d. Had difficulty performing the work or other activities (for example, it took extra effort)	☐1	☐2	☐3	☐4	☐5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b. Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c. Did work or other activities less carefully than usual	☐1	☐2	☐3	☐4	☐5

6. **During the <u>past 4 weeks</u>, to what extent has your <u>physical health or emotional problems</u> interfered with your normal social activities with family, friends, neighbors, or groups?**

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. **How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?**

None	Very mild	Mild	Moderate	Severe	Very Severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. **During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	☐1	☐2	☐3	☐4	☐5
b. Have you been very nervous?	☐1	☐2	☐3	☐4	☐5
c. Have you felt so down in the dumps that nothing could cheer you up?	☐1	☐2	☐3	☐4	☐5
d. Have you felt calm and peaceful?	☐1	☐2	☐3	☐4	☐5
e. Did you have a lot of energy?	☐1	☐2	☐3	☐4	☐5
f. Have you felt downhearted and depressed?	☐1	☐2	☐3	☐4	☐5
g. Did you feel worn out?	☐1	☐2	☐3	☐4	☐5
h. Have you been happy?	☐1	☐2	☐3	☐4	☐5
i. Did you feel tired?	☐1	☐2	☐3	☐4	☐5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐1	☐2	☐3	☐4	☐5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

THANK YOU FOR COMPLETING THESE QUESTIONS!

10.9. Appendix 9: Hauser Ambulation Index (HAI)

□ 0 = Asymptomatic; fully active.

□ 1 = Walks normally, but reports fatigue that interferes with athletic or other demanding activities.

□ 2 = Abnormal gait or episodic imbalance; gait disorder is noticed by family and friends; able to walk 25 feet (8 meters) in 10 seconds or less.

□ 3 = Walks independently; able to walk 25 feet in 20 seconds or less.

□ 4 = Requires unilateral support (cane or single crutch) to walk; walks 25 feet in 20 seconds or less.

□ 5 = Requires bilateral support (canes, crutches, or walker) and walks 25 feet in 20 seconds or less; *or* requires unilateral support but needs more than 20 seconds to walk 25 feet.

□ 6 = Requires bilateral support and more than 20 seconds to walk 25 feet; may use wheelchair[1] on occasion.

□ 7 = Walking limited to several steps with bilateral support; unable to walk 25 feet; may use wheelchair[1] for most activities.

□ 8 = Restricted to wheelchair; able to transfer self independently.

□ 9 = Restricted to wheelchair; unable to transfer self independently.

[1]The use of a wheelchair may be determined by lifestyle and motivation. It is expected that patients in Grade 7 will use a wheelchair more frequently than those in Grades 5 or 6. Assignment of a grade in the range of 5 to 7, however, is determined by the patient's ability to walk a given distance, and not by the extent to which the patient uses a wheelchair.

10.10. Appendix 10: Optic Spinal Impairment Score (OSIS)

Visual Acuity (VA)

0 Normal
1 Scotoma but VA (corrected) better than 20/30
2 VA 20/30 - 20/59
3 VA 20/60 - 20/100
4 VA 20/ 101 - 20/200
5 VA 20/201 - 20/800
6 Count fingers only
7 Light perception only
8 No light perception

Motor Function

0 Normal
1 Abnormal signs (hyperreflexia, Babinski sign) without weakness
2 Mild weakness (Medical Research Council [MRC] grade 5- or 4+) in affected limb(s)
3 Moderate weakness (grade 3 or 4) in 1 or 2 upper motor neuron (UMN) muscles in affected limb(s)
4 Moderate weakness (grade 3 or 4) in 3 UMN muscles in affected limb(s)
5 Severe weakness (grade 2) in 1 or more muscles in affected limb(s)
6 Some plegic (grade 0 or 1) muscles in 1 or more limbs
7 Plegia (grade 0 or 1) of all muscles in 1 or more limbs

Sensory Function

0 Normal
1 Mild decrease in vibration
2 Mild decrease in pinprick/temperature/proprioception or moderate decrease in vibration
3 Moderate decrease in touch/pin/proprioception or essentially lost vibration sense
4 Loss of all sensory modalities
5 Unknown

Sphincter Function

0 Normal
1 Mild urinary urgency or hesitancy; constipation
2 Moderate urinary urgency, hesitancy, or retention of bladder or bowel, infrequent urinary incontinence (less than once/week)
3 Frequent incontinence or retention requiring intermittent bladder catheterization or aggressive (manual) bowel assistance
4 Indwelling urinary catheter or absence of sphincter control
5 Unknown

10.11. Appendix 11: Relapse Severity

Table 12: Relapse Severity as Measured by Optic Spinal Impairment Scale

Optic Neuritis		
Visual Acuity Subscale Score (taken from the eye with the largest change at the time of the event)		**Relapse Descriptor**
Pre-Relapse	**Post-Relapse**	
0-1	0-2	Minor
0-1	3+	Major
2-7	Increase by 1 point	Minor
2-7	Increase by ≥ 2 points	Major
Transverse Myelitis		
Motor Subscale Score		**Relapse Descriptor**
Pre-Relapse	**Post-Relapse**	
0-1	0-2	Minor
0-1	3+	Major
2-6	Increase by 1 point	Minor
2-6	Increase by ≥ 2 points	Major
Sensory Subscale Score		**Relapse Descriptor**
Based on proprioceptive loss only	If severe loss in ≥ 1 or more limbs with prior normal function or with mild proprioceptive loss	Major

10.12. Appendix 12: Columbia Suicide Severity Rating Scale (C-SSRS)-Screening/Baseline

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** _____ (*Type # (1-5)*) _____ (*Description of Ideation*) Past X Months - ***Most Severe Ideation:*** _____ (*Type # (1-5)*) _____ (*Description of Ideation*)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt. *There does not have to be any injury or harm*, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. *Have you made a suicide attempt?* *Have you done anything to harm yourself?* *Have you done anything dangerous where you could have died?* *What did you do?* *Did you_____ as a way to end your life?* *Did you want to die (even a little) when you_____?* *Were you trying to end your life when you _____?* *Or did you think it was possible you could have died from_____?* *Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?* (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes** **No** ☐ ☐ Total # of Attempts _____ **Yes** **No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. *Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?* If yes, describe:	**Yes** **No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. *Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?* If yes, describe:	**Yes** **No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). *Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?* If yes, describe:	**Yes** **No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** **No** ☐ ☐
Suicide:	**Yes** **No** ☐ ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

10.13. Appendix 13: Columbia-Suicide Severity Rating Scale (C-SSRS)-Since Last Visit

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

Version 1/14/09

10.14. Appendix 14: Management of Potential Infusion-Associated Adverse Events During Study Drug Administration

Intravenous and infusion-associated reactions are a potential risk with the use of mAbs; these reactions can be nonimmune or immune mediated (eg, hypersensitivity reactions). Signs and symptoms may include headache, fever, facial flushing, pruritus, myalgia, nausea, chest tightness, dyspnea, vomiting, erythema, abdominal discomfort, diaphoresis, shivers, hypertension, lightheadedness, hypotension, palpitations, and somnolence. Signs and symptoms of hypersensitivity or allergic reactions may include hives, swollen face, eyelids, lips, or tongue, or trouble with breathing.

All administration-, IV-, and infusion-associated reactions will be reported to the Investigator and qualified designee. The Investigator and qualified designee are responsible for detecting, documenting, and recording events that meet the definition of AE or SAE and remain responsible for following up events that are serious, considered related to the study drug, or study procedures; or that caused the patient to discontinue the study drug (Section 7).

Definitions and procedures for recording, evaluating, follow-up, and reporting AEs and SAEs are outlined in Section 10.3.

Patients who experience a reaction during the administration of study drug should be treated according to institutional guidelines.

Patients who experience a severe reaction during administration of study drug resulting in discontinuation of study drug should undergo all scheduled safety, PK, and PD evaluations required by the protocol. The Sponsor must be notified within 24 hours of any infusion reaction requiring interruption or discontinuation of study drug. All AEs that may indicate an infusion related response will be graded according to the CTCAE v5.0 or higher.

If anaphylaxis occurs according to the criteria listed in Table 13, then administration of SC epinephrine (1/1000, 0.3 mL to 0.5 mL, or equivalent) should be considered. In the case of bronchospasm, treatment with an inhaled beta agonist also should be considered. Patients administered an antihistamine for the treatment or prevention of an infusion reaction should be given appropriate warnings about drowsiness and impairment of driving ability before being discharged from the center.

Table 13: Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any 1 of the following 3 criteria is fulfilled:
• Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula), and at least 1 of the following: o Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) o Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
• Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours): o Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips/tongue/uvula) o Respiratory compromise (eg, dyspnea, wheeze/bronchospasm, stridor, reduced PEF, hypoxemia) o Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence) o Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
• Reduced BP after exposure to known allergen for that patient (minutes to several hours): o Systolic BP of less than 90 mmHg or greater than 30% decrease from that patient's baseline

Abbreviations: BP = blood pressure; PEF = peak expiratory flow.
Source: (Sampson, 2006)

10.15. Appendix 15: Identification of Cases of Interest

A Case of Interest is an event judged by the Treating Physician to not be an On-trial Relapse (ie, it is not an Investigator confirmed On-trial Relapse), but which meets the following criteria to be considered a Case of Interest and submitted to the RAC for adjudication:

- Patients who were seen by the Treating Physician for a 24- to 48-hour relapse evaluation visit and where the Treating Physician concluded that an On-trial Relapse did not occur, OR
- A sentinel AE (eg, AEs of: weakness, sensory changes, especially in a dermatomal distribution, characteristic visual changes of NMOSD, or pseudo exacerbation of NMOSD) AND either:
    - An MRI was performed contemporaneously OR
    - Neurologic symptoms were treated (by hospitalization or IVMP) OR
    - Contemporaneous objective worsening of the Treating Physician's Neurologic Examination (defined by answer of "worse" to clinically meaningful change question).

Cases of Interest involving a patient seen for a potential relapse where the Treating Physician concluded that an On-trial Relapse did not occur will be identified in real-time as they occur throughout the study.

Additionally, periodically throughout the study, searching for sentinel AEs associated with neurologic changes on the Treating Physician's Neurologic Examination, MRI, and/or treatment with hospitalization or IVMP will be done. This process will occur mid study, at 25% completion, 75% completion, and the end of the study. A meeting to review potential cases will be held and attended by at least one representative for Medical, Biostatistics, and Clinical Operations with optional attendance from Data Management. Events reviewed in this meeting that do not meet the definition of a Case of Interest will be recorded along with a brief description of the reason they do not meet the criteria for a Case of Interest.

Case of Interest Sentinel AE term identification

Review of the AE term list to identify sentinel events will be done at least 4 times during the study. This list will be updated based on a review of SAEs, MRI indications, neurologic examination changes and treatments associated with AEs. At the time the study is 80% complete a final review will be conducted to update terms and to search AEs again to identify all sentinel AEs in the search term list.

The following AE terms are examples of ones to be flagged as sentinel AEs and used to identify Cases of Interest.

The final list of AE terms will be maintained by Biostatistics in the SAS environment.

Table 14 List of Example AE Terms to be Flagged as Sentinel AEs and Used to Identify Cases of Interest

Abdominal discomfort	Hemiparaesthesia	Neuralgia
Abdominal pain	Hiccups	Neuromyelitis optica spectrum disorder
Abdominal pain lower	Hyperaesthesia	Optic neuritis
Abdominal pain upper	Hypersensitivity	Pain
Ataxia	Hypoaesthesia	Pain in extremity
Back pain	Hypoaesthesia oral	Paraesthesia
Bladder disorder	Micturition disorder	Photophobia
Burning sensation	Micturition urgency	Pruritus
Chest pain	Muscle contractions involuntary	Pruritus generalised
Constipation	Muscle contracture	Sensory disturbance
Dysaesthesia	Muscle spasms	Skin burning sensation
Dysphonia	Muscle spasticity	Spinal pain
Dysuria	Muscle tightness	Tinnitus
Eructation	Muscular weakness	Uhthoff's phenomenon
Eye pain	Musculoskeletal discomfort	Urinary retention
Fall	Musculoskeletal pain	Urinary tract disorder
Flank pain	Musculoskeletal stiffness	Vision blurred
Gait disturbance	Myalgia	Visual acuity reduced
Groin pain	Nausea/Vomiting	Visual impairment
Hemianopia	Neck pain	

10.16. Appendix 16: Remote Source Data Verification During COVID-19 Pandemic

To ensure the rights, safety, and well-being of study patients, as well as the integrity of the trial and its data during the COVID-19 pandemic, when onsite study monitoring activities are restricted, remote source data verification (rSDV) may be employed wherever permitted by local regulations.

Study ALXN1210-NMO-307 is a Phase 3, pivotal study in patients with NMOSD, a rare and devastating neurological disease. Alexion has assessed that the inability to complete ongoing SDV could pose a risk to the robustness of the study data. Delaying ongoing verification of key efficacy (primary and secondary) endpoints and important safety endpoints could result in late identification of incorrect or missing data, which could impact the integrity of the study data.

Remote SDV will be carried out in written agreement with the Investigator and, if applicable, the institution, under conditions ensuring adequate data protection and patients' rights. Depending on local regulation and agreement with the site Investigator and institution preference, rSDV may be conducted through direct and controlled read-only monitor access to institution electronic medical records systems, passive access to source documents via live image transmission, and/or sharing of redacted copies of source documents via a secure, validated, and access-restricted system. Regarding the electronic sharing of redacted copies of source documents, the following requirements must be followed:

- Scanned or electronic documents to be uploaded (as PDF, jpeg, or other image format) that are of sufficient resolution to ensure readability, in black and white or color.
- To ensure completeness of the shared content, the monitor will prepare a written request to the investigative site listing the source data needed to conduct rSDV and will perform a quality check on the list of documents shared by the site against the list of requested source data.
- Site staff must perform a quality check ensuring source documents are redacted before making them available to monitors. A data breach management policy and a security team will be in place to identify violations and to ensure correct and timely action.
- To prevent loss of or unauthorized access to source data, investigative site personnel will need to actively grant access to their specific monitor. The monitor will only have viewing rights, thereby preventing loss, alteration, or download of source data.
- Traceability of pseudonymized documents reviewed remotely will be kept by the monitor for verification onsite.

The detailed scope of rSDV will be outlined in supporting study plans (eg, Clinical Monitoring Plan). Conduct of rSDV will only be performed during the COVID-19 pandemic.

The following data will require rSDV to ensure oversight of patients' safety and integrity of the trial data.

Data	**Assessments**
Safety	Eligibility assessments, investigational product exposure, adverse events, concomitant medications and non-drug therapies, laboratory assessments, ECGs, vital signs, C-SSRS
Efficacy Endpoints	EDSS, OSIS, HAI, EQ-5D, SF-36, ophthalmologic examination, neurologic examination, On-trial Relapse evaluation

10.17. Appendix 17: COVID-19 Risk Assessment

Neuromyelitis optica spectrum disorder can cause irreversible morbidity and even mortality, if untreated. As such, and due to the limited number of available treatment options, the benefit a patient may receive from joining an investigational study with a therapeutic treatment is potentially significant. The fact that Study ALXN1210-NMO-307 is open-label and every patient is treated with ravulizumab also contributes to the potential benefit a patient may derive from participating in the study. Given that treatment for NMOSD does involve immunosuppression, there is a theoretical concern that the risk for infection may be higher than in patients not receiving immunosuppressants. However, there is no specific data to further inform this risk. The site Investigator will therefore balance the risk/benefit considerations in the study patient taking these factors into account.

The potential risks identified, and mitigation measures put in place in light of the COVID-19 pandemic are provided in Table 15.

Table 15: Potential Risks and Mitigation Measures due to COVID-19

Risks Category	Summary of Data/ Rationale for Risk	Mitigation Strategy
Potential risks		
Healthcare institution availability for non-COVID-19 related activities	COVID-19 pandemic may impact the workload of healthcare institutions globally and may reduce staff availability to perform non-urgent activities and non-COVID-19 related activities.	During the time that the COVID-19 pandemic is active, Alexion will not open study sites or enroll new patients at sites unless the sites have the resourcing and capabilities to implement the study per protocol.

Table 15: Potential Risks and Mitigation Measures due to COVID-19

Risks Category	Summary of Data/ Rationale for Risk	Mitigation Strategy
Data quality and integrity	Lack of availability of site personnel to perform study assessments and capture study specific data in a timely manner and to maintain adequate quality standards. Lack of availability of site personnel to ensure adequate and continuous chain of custody, storage conditions, and monitoring for investigational product and biological samples. Inability of study monitors and quality personnel to conduct in-person visits to exercise adequate oversight of study execution at investigational sites. Missing data (COVID-19 pandemic may impact study visit schedules, and increase missed visits and/or patient study discontinuations inadvertently resulting in missing data [eg, for protocol-specified procedures]).	During the time that the COVID-19 pandemic is active, Alexion will only open study sites that report enough personnel capacity to sufficiently conduct clinical study-related activities. During this timeframe, site capacity will be reviewed by the site Investigator and the study Medical Monitor prior to Screening. Each site is also evaluated for the capacity to perform remote monitoring visits and remote source data verification. During the time that the COVID-19 pandemic is active, it will be important to capture specific information in the eCRF that explains the reason the data is missing (eg, missed study visits or patient study discontinuations due to COVID-19).

Abbreviations: COVID-19 = coronavirus disease 2019; eCRF = electronic case report form

10.18. Appendix 18: Protocol Amendment History

The protocol amendment summary of changes table for the current amendment is located directly before the Table of Contents.

DOCUMENT HISTORY	
Document	**Summary of Key Changes**
Amendment 1.2 (United Kingdom) 07 Jun 2021	The purpose of this country-specific amendment was to include coronavirus disease 2019 (COVID-19) risk assessment and COVID-19 vaccine risk assessment language in the appendices.
Amendment 1.1 (Germany) 28 Apr 2021	The purpose of this country-specific amendment was to update the safety criteria for study termination, and to include language for remote source data verification during the COVID-19 pandemic, to comply with German regulation.
Amendment 1.0 (Global) 06 Jul 2020	The main purpose of this amendment was to provide updated criteria and an updated definition for the End of Primary Treatment (EOPT) Period, to establish the modified Full Analysis Set as the primary analysis set for efficacy endpoints, to add biweekly phone visits, to provide guidance on regional enrollment limits, and to provide further instruction on off-site visits, infusion reactions, and minor updates on the statistical analysis and operational aspects of the protocol.
Original Protocol (Global) 12 Aug 2019	Not applicable

10.19. Appendix 19: Abbreviations

Abbreviation	Definition
Ab	antibody
ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
aHUS	atypical hemolytic uremic syndrome
ANCOVA	analysis of covariance
AQP4	aquaporin-4
ARR	annualized relapse rate
AZA	azathioprine
B	baseline (sample)
BP	blood pressure
C5	complement component 5
CFR	Code of Federal Regulations
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
COVID-19	Coronavirus Disease 2019
CNS	central nervous system
CRF	case report form
CSF	cerebrospinal fluid
C-SSRS	Columbia-suicide severity rating scale
CTCAE	Common Terminology Criteria for Adverse Events
D	day
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
ED	early discontinuation
EDC	electronic data capture
EDSS	expanded disability status scale
EOPT	End of Primary Treatment
EOS	End of Study
EOT	End of Treatment
EQ-5D	European Quality of Life Health 5-item questionnaire
EQ VAS	European Quality of Life Visual Analog Scale
EuroQoL	European Quality of Life
FAS	full analysis set
FDA	Food and Drug Administration
FS	functional system
FSS	functional system scores

Abbreviation	Definition
FU	Follow-up
GCP	Good Clinical Practice
gMG	generalized myasthenia gravis
HAI	Hauser Ambulation Index
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormonal replacement therapy
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IL-6	interleukin 6
IMP	Investigational medicinal product
IPND	International Panel for NMO Diagnosis
IRB	Institutional Review Board
IST	immunosuppressive therapy
IV	intravenous
IVIg	intravenous immunoglobulin
IVMP	intravenous methylprednisolone
L	low
MAA	marketing authorization application
mAb	monoclonal antibody
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MMF	mycophenolate mofetil
MRC	Medical Research Council
MRI	magnetic resonance imaging
MS	multiple sclerosis
MTX	methotrexate
N	normal
NA	not applicable
NfL	neurofilament light chain
NMO	neuromyelitis optica
NMOSD	neuromyelitis optica spectrum disorder
OCT	Optical Coherence Tomography
ON	optic neuritis
OSIS	Optic Spinal Impairment Score
P	postdose (sample)
PD	pharmacodynamic(s)
PE	plasma exchange

Abbreviation	Definition
PI	Principal Investigator
PK	pharmacokinetic(s)
PKPDAS	Pharmacokinetic and Pharmacodynamic Analysis Set
PNH	paroxysmal nocturnal hemoglobinuria
PP	plasmapheresis
PT	primary treatment
q2w	every two weeks
q8w	every eight weeks
QoL	quality of life
QT	interval between the start of the Q wave and the end of the T wave in an ECG
QTc	corrected QT interval
RAC	Relapse Adjudication Committee
RBC	red blood cell
RD	relapse day
RNA	ribonucleic acid
RR	respiratory rate
rSDV	remote source data verification
SAE	serious adverse event
SAP	statistical analysis plan
SF	short form health survey
SoA	schedule of activities
SOC	System Organ Class
SUSAR	suspected unexpected serious adverse reactions
T	Trough
TAC	tacrolimus
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TM	transverse myelitis
UMN	upper motor neuron
USPI	United States Prescribing Information
VA	visual acuity
VAS	visual analogue scale
VF	Visual Fields
W	week(s)
WBC	white blood cell
WHODrug	World Health Organization Drug Dictionary
WOCBP	woman of childbearing potential

11. REFERENCES

Bethoux F, Bennett S. Evaluating Walking in Patients with Multiple Sclerosis: Which Assessment Tools Are Useful in Clinical Practice? International Journal of MS Care. 2011;13(1):4-14.

Bichuetti DB LdOE, Oliveira DM, Amorin de Souza N, Gabbai AA. Neuromyelitis optica treatment: analysis of 36 patients. Archives of neurology. 2010;67(9):1131-1136.

Diebolder CA BF, de Jong RN, et al. Complement is activated by IgG hexamers assembled at the cell surface. Science. 2014;343(6176):1260-1263.

Flanagan EP CP, Weinshenker BG, et al. Epidemiology of aquaporin-4 autoimmunity and neuromyelitis optica spectrum. Ann Neurol 2016;79:775-783.

Ghezzi A BR, Martinelli V. Clinical characteristics, course and prognosis of relapsing Devic's neuromyelitis optica. J Neurol. 2004;251:47-52.

Hauser SL, Dawson DM, Lehrich JR, et al. Intensive immunosuppression in progressive multiple sclerosis. A randomized, three-arm study of high-dose intravenous cyclophosphamide, plasma exchange, and ACTH. N Engl J Med. 1983;308(4):173-180.

Heinze G, Schemper M. A solution to the problem of monotone likelihood in Cox regression. Biometrics. 2001;57(1):114-119.

Hinson SR MA, Fryer JP, et al. Prediction of neuromyelitis optica attack severity by quantitation of complement-mediated injury to aquaporin-4-expressing cells. Arch Neurol. 2009;66(9):1164-1167.

Jacob A MM, Weinshenker BG, et al. Treatment of neuromyelitis optica with mycophenolate mofetil: retrospective analysis of 24 patients. Archives of neurology. 2009;66(9):1128-1133.

Jarius S RK, Wildemann B, et al. Contrasting disease patterns in seropositive and seronegative neuromyelitis optica: a multicentre study of 175 patients. J Neuroinflammation 2012;9:14.

Keltner JL, Johnson CA, Spurr JO, Beck RW. Comparison of central and peripheral visual field properties in the Optic Neuritis Treatment Trial. American Journal of Ophthalmology. 1999;128(5):543-553.

Kitley J LM, Nakashima I, et al. Prognostic factors and disease course in aquaporin-4 antibody-positive patients with neuromyelitis optica spectrum disorder from the United Kingdom and Japan. Brain: a journal of neurology. 2012;135:1834-1849.

Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983;33(11):1444-1452.

Nytrova P, Potlukova E, Kemlink D, et al. Complement activation in patients with neuromyelitis optica. J Neuroimmunol. 2014;274(1-2):185-191.

Pandit L AN, Apiwattanakul M, et al. Demographic and clinical features of neuromyelitis optica: A review. Mult Scler. 2015;21(7):845-853.

Papadopoulos MC VA. Aquaporin 4 and neuromyelitis optica. Lancet Neurol. 2012;11(6):535-544.

Pittock SJ BA, Fujihara K, Kim HJ, Levy M, Palace J, Nakashima I, Terzi M, Totolyan N, Viswanathan S, Wang K-C, Pace A, Fujita KP, Armstrong R, and Wingerchuk DM. Eculizumab in Aquaporin-4–Positive Neuromyelitis Optica Spectrum Disorder. N Engl J Med. 2019.

Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117(2):391-397.

Schrag A, Selai C, Jahanshahi M, Quinn NP. The EQ-5D—a generic quality of life measure—is a useful instrument to measure quality of life in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry. 2000;69(67-73):67.

Stewart AL, Hays RD, Ware JE, Jr. The MOS short-form general health survey. Reliability and validity in a patient population. Med Care. 1988;26(7):724-735.

Trebst C JS, Berthele A, et al. Update on the diagnosis and treatment of neuromyelitis optica: recommendations of the Neuromyelitis Optica Study Group (NEMOS). J Neurol. 2014;261(1):1-16.

Verkman AS. Aquaporins in clinical medicine. Annu Rev Med. 2012;63:303-316.

Ware J, Sherbourne C. The MOS 36-item short-form health survey (SF-36): I. conceptual framework and item selection. Med Care. 1992;30:473-483.

Weinshenker BG, Barron G, Behne JM, et al. Challenges and opportunities in designing clinical trials for neuromyelitis optica. Neurology. 2015;84(17):1805-1815.

Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology. 2015;85(2):177-189.

Wingerchuk DM LV, Pittock SJ, Lucchinetti CF, Weinshenker BG. Revised diagnostic criteria for neuromyelitis optica. Neurology. 2006;66(10).